J Korean Med Sci 1998; 13: 207-10
ISSN 1011-8934

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Malignant Mixed Müllerian Tumor (homologous type) of the Adnexa with Neuroendocrine Differentiation : A Case Report

Malignant mixed müllerian tumors (MMMT) are unusual neoplasms occuring mostly in the uterus. In the ovary, they are very rare and represent fewer than 1% of all ovarian malignancies; in the salpinx, they are even rarer than those of the ovary. We report a carcinosarcoma of the left adnexa having features of neuroendocrine differentiation in a 69-year-old female. The tumor contained both adenocarcinoma and squamous cell carcinoma having clear cell change admixed with an undifferentiated malignant mesenchymal component. The sarcoma components consisted of spindle cells, small-round cells and bizarre giant cells mimicking rhabdomyoblast. Almost all of the carcinomatous glandular components and some foci of the squamous cell and undifferentiated carcinomatous components were focal positive for S-100 protein, chromogranin, neuron specific enolase, synaptophysin and Leu-7. Electron microscopy revealed membrane-bound neurosecretory granules in the cytoplasm of some glandular epithelial cells. Histologically, the tumor involved the left adnexa, abdominal peritoneum, surface of the bladder dome, omentum and left external iliac lymph node (stage IIIc).

Key Words : *Mixed tumor, muellerian; Neuroendocrine differentiation; Adnexa uteri*

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Received : August 19, 1997
Accepted : November 12, 1997

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INTRODUCTION

Malignant mixed müllerian tumors (MMMTs) are uncommon neoplasms of the female genital tract that histologically consist of malignant epithelial and stromal components (1). They are detected in decreasing frequency in the uterine corpus, uterine cervix, vagina, ovaries, and fallopian tubes (2). MMMTs of the ovary are very rare, comprising less than 1% of ovarian malignancies; in the salpinx they are much rarer than those of the ovary (1). Since the first report of neuroendocrine differentiation in MMMTs (3), about 17% of reported MMMTs have exhibited neuroendocrine differentiation (4). The MMMTs with neuroendocrine differentiation exhibit a tendency toward more aggressive behavior (4). We report a case of MMMT with neuroendocrine differentiation of the left adnexa with a brief review of the literature.

CASE REPORT

A 69-year-old female gravida 2, para 2, was admitted to Chosun University Hospital via a local OB-GY clinic because of a mass in the left lower abdomen. Physical examination was unremarkable except for a man's fist-sized mass in the left adnexa. There were no other symptoms reported, and she had previously been well. There was no history of irregular bleeding. Laboratory tests showed within normal ranges for CBC, LFT, urinalysis, but increased levels for CA 125 (64.7 u/ml) and CA19-9 (17.2 u/ml). The ultrasonogram of the abdomen and pelvis showed a 10×7 cm sized mass in the left adnexa. An exploratory laparotomy with vertical incision was performed under the impression of ovarian malignancy and approximately 100 ml of serous ascites was present in the pelvic cavity. Ascitic fluid was sent for cytologic examination. There was a $10 \times 7 \times 5$ cm sized tumor mass in the left adnexa and it was adherent to the perimetrium of the uterine corpus. The left salpinx and ovary were not discernible because of the tumor adhesion so, we were not able to detect whether its origin was from the salpinx or the ovary. The lower part of the omentum, surface of the vesical dome, ascending colon, sigmoid colon, rectum and peritoneum were adherent to the main tumor mass. The left external iliac lymph nodes were noted. The patient underwent total hysterec-

Fig. 1. Cut section along the long axis shows tumor mass adherent to the perimetrium of the uterine corpus and the left adnexa.

tomy with bilateral salpingo-oophorectomy, total omentectomy and pelvic lymph node dissection. The cut surface of the mass revealed hemorrhagic necrosis with multiple small cystic changes containing serous fluid. The tumor involved only the perimetrium and not the myometrium (Fig. 1). The tumor was proved a carcinosarcoma of the left adnexa involving the abdominal peritoneum, surface of the vesical dome, omentum and the left external iliac lymph node. Cytologic examination of the ascitic fluid was negative for malignancy. The epithelial components contained adenocarcinoma, squamous cell carcinoma having clear cell change, serous and undifferentiated carcinoma. The adenocarcinoma consisted of poorly differentiated endometrioid and serous tumors (Fig. 2). The carcinomatous portions were positive for cytokeratin and epithelial membrane antigen. Almost all of the carcinomatous glandular components and some foci of the squamous cell and undifferentiated carcinomatous components were focal positive for S-100 protein, chromogranin, neuron specific enolase, synaptophysin and Leu-7 (Fig. 3). Periodic acid-Schiff (PAS) and mucicarmine stains revealed luminal, but not cytoplasmic mucin in the adenocarcinoma elements. PAS, alcian blue at pH 2.5 and mucicarmine stains revealed negative reaction in the cytoplasm of the clear cells. The sarcomatous components consisted of high cellular spindle cells, compact small round cells and bizarre giant cells in the background of loose myxoid vascular stroma (Fig. 4). The scattered round to polygonal or tadpole-like cells having deeply eosinophilic cytoplasm in the small round cells mimicked rhabdomyoblast but which were negative for desmin and myoglobin. Electron microscopy revealed membrane-bound neurosecretory granules in the cytoplasm of some glandular epithelial cells (Fig. 5). According to the results of the immunohistochemical and special staining and electron microscopic observation we conclude that the lesion was finally proved to be a homologous type of MMMT with neuroendocrine differentiation of the left adnexa (clinical stage IIIc). Flow cytometric analysis revealed aneuploidy pattern (DNA index:1.62). She was treated with a single cycle of postoperative cisplatin/adriamycin combination chemotherapy but, further chemotherapy was not given because of the patient's refusal. She remains well without evidence of disease 4 months after operation.

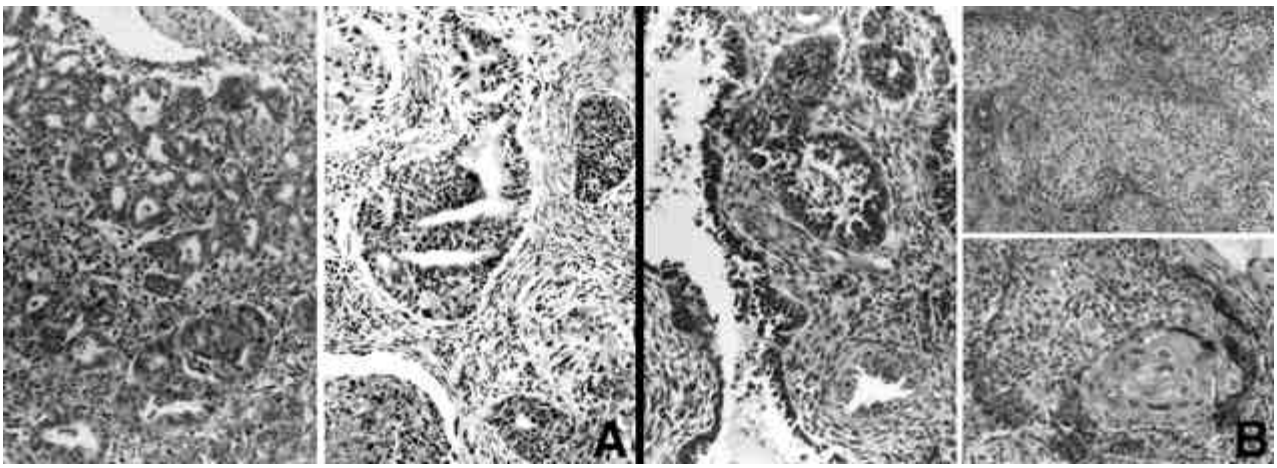

Fig. 2. A: Endometrioid adenocarcinoma consists of small tubular pattern (left) and glandular pattern with squamous differentiation (right) (Hematoxylin-eosin stain, ×100). B: Serous differentiated adenocarcinoma (left) and squamous cell carcinoma having clear cell change (right) are noted (Hematoxylin-eosin stain, ×100; right upper, ×40).

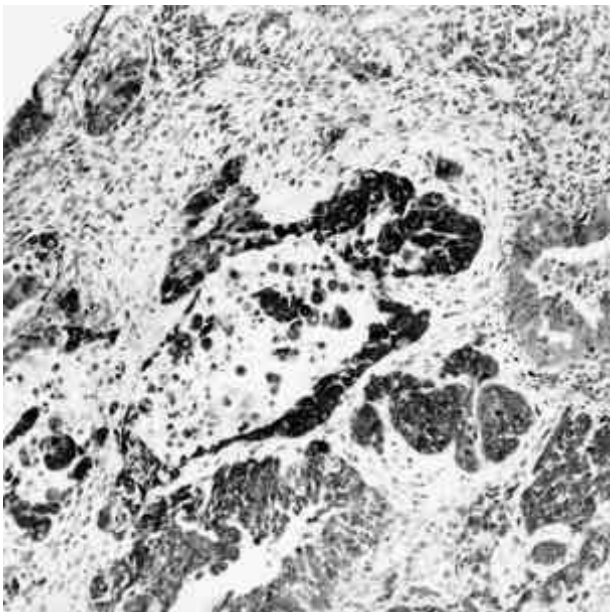

Fig. 3. A portion of neuroendocrine differentiation shows positive staining for the chromogranin in the epithelial components (ABC method, ×100).

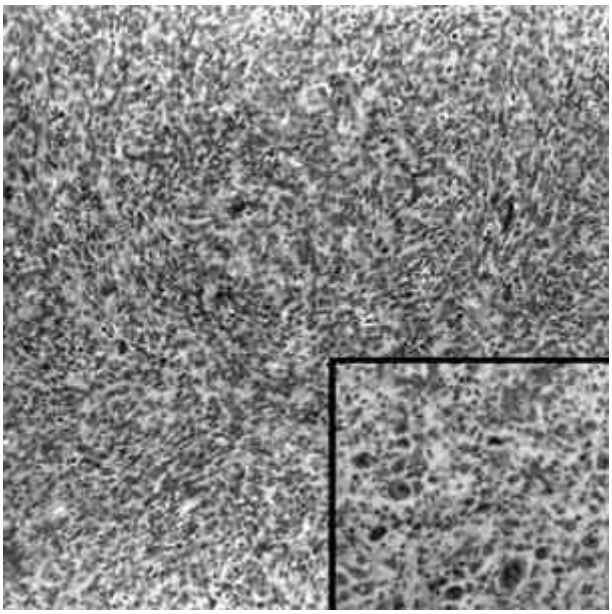

Fig. 4. Sarcomatous component consists of high cellular spindle cells and giant cells with storiform growth pattern. Inset: Plump eosinophilic cytoplasm with myxoid background mimicking rhabdomyoblastic differentiation (Hematoxylin-eosin stain, ×100).

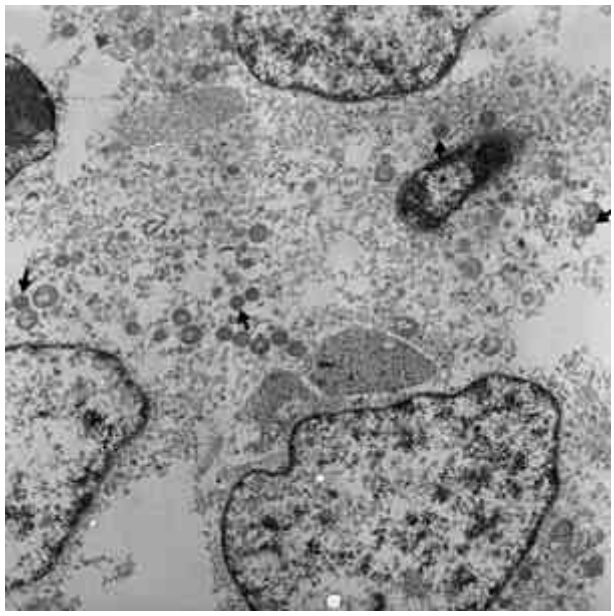

Fig. 5. Electron microscopy shows the membrane-bound neurosecretory granules (arrows) in some tumor cells of the adenocarcinomatous portions (uranyl acetate and lead citrate, ×10,000)

DISCUSSION

Tumors composed of an admixture of malignant epithelial and stromal components are unusual neoplasms which are generally classified with MMMTs in the female genital tract. MMMTs occur almost exclusively in postmenopausal women, with an average in the early 60's (5). These tumors most commonly arise in the endometrium accounting for 1.5% of all uterine malignancies (6). Less commonly, similar tumors arise in the ovary, cervix, fallopian tube, and vagina (4, 7-10). The ovary and salpinx are the least common sites for MMMTs, our case occurred in the adnexa. The epithelial components were endometrioid adenocarcinoma, squamous cell carcinoma, serous carcinoma and undifferentiated carcinoma. The squamous cell carcinoma were mostly well differentiated, but focally differentiated into clear cell. The tubular structures staining for neuroendocrine markers have to distinguish neuroendocrine differentiation from neuroectodermal differentiation. But, the luminal and not cytoplasmic staining for PAS and mucicarmine stains distinguished them from neuroectodermal differentiation bearing primitive neurotubular structures (11). Almost all portions of the carcinoma elements in our case showed focal neuroendocrine differentiation. Manivel et al. (3) first reported the neuroendocrine differentiation of MMMTs. George et al. (4) reported it as a predictor of a more rapidly fatal course. About 17% (8/47) of MMMTs exhibit neuroendocrine differentiation (4), which is not high in view of the relatively common presence of endocrine features in a variety of poorly differentiated carcinomas (12-14). In the other organs (15-19) carcinoma with neuroendocrine differentiation has poor prognosis. The MMMTs with neuroendocrine differentiation

exhibit a tendency toward a more rapidly fatal course, with five of six patients dying within 9 months however, this has no statistically significant influence on survival (4).

The tumors may be subdivided on the basis of the nature of the stroma into homologous and heterologous type. The present case had no elements extrinsic to the uterus, so it was homologous type. About 33% of the tumors have been homologous type, and the most common heterologous element has been rhabdomyosarcoma (4, 7). Some early studies (20-22) have correlated a worse prognosis with heterologous differentiation, particularly when it was rhabdomyoblastic in type; however, in other studies (4, 23, 24) histologic subclassification has not been prognostically significant.

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