

A Case Report of Malignant Müllerian Mixed Tumor of the Uterus

Al Muktafi SADI¹, Yoshisada SHINGAKI², Masaya KIYUNA¹,
Tooru TAMAMOTO¹, Takayoshi TODA^{1,2}, Bilquis QURESHI³, and Tadashi IHA³

The Department of Clinical Laboratory Medicine, School of Medicine¹, Diagnostic Laboratory, University Hospital², and Department of Obstetrics and Gynecology, School of Medicine³, University of the Ryukyus, Okinawa, Japan

We experienced a case of malignant Müllerian mixed tumor of the uterus of a 58-year-old female. We performed an immunohistochemical study in order to analyze the expression of various antigens in different elements of this tumor. Keratin, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA) showed strong positive results in epithelial component, while EMA also showed positive results in some areas of sarcomatous elements. On the other hand, vimentin and S-100 gave strong positive result in non-epithelial component, but also was positive to some extent in epithelial component in this tumor. Immunohistochemical method was useful to differentiate the different components of this tumor. However, EMA, Vimentin and S-100 showed some unusual results. This discrepancy may indicate a change in the nature of tumor cells due to 'microenvironmental' factors such as hormones and vitamins. Therefore, careful evaluation is necessary to interpret the immunohistochemical results in surgical pathology.

Key words: Malignant Müllerian mixed tumor, Uterus,

Introduction

Malignant Müllerian mixed tumor of the female genital tract is a rare neoplasm of uncertain histogenesis. The origin of this tumor is said to be Müllerian, and the terms 'malignant Müllerian mixed tumor' or 'malignant mesodermal mixed tumor' (MMMT) have been applied to uterine neoplasms which are composed of mixture of malignant epithelial and mesenchymal elements¹⁾. About 50% of the uterine sarcomas accounts for MMMT²⁾. The patients are usually elderly postmenopausal and a large proportion of the patients had a prior history of having radiotherapy^{3,4)}. It arises most frequently in the uterine corpus, but also occurs rarely at other sites such as the ovary, vagina and pelvic wall⁵⁾. Routine light microscopy only is sometimes difficult to recognize the different components of MMMT. In undifferentiated cases immunostaining is a helpful method to indentify both an epithelial and a mesenchymal component. Here we report a case of malignant Müllerian mixed tumor with immunohistochemical study.

Case report

A 58-year-old female came to our university hospital on December 9, 1992 with a complaint of feeling a mass in the abdomen for two months. She had a previous history of vaginal carcinoma of grade III b seven years ago, that was totally regressed after complete radiation therapy. She had neither pain nor history of genital bleeding. And she had no other systemic diseases except mild diabetes.

On examination an elastic hard movable mass was found in the lower abdomen. Per vaginal examination revealed smooth vaginal wall and a closed cervix. The mass was confined to the body of the uterus. Ultrasonography showed a 8x6 cm-sized partially solid and cystic mass in the uterus. Computed Tomography showed high density in solid and low density in cystic area, respectively. By Magnetic Resonance Image it was confirmed that the mass is intrauterine and no involvement of the adnexae was found. The mass became reduced after drainage of brownish fluid by external os puncture. By hysteroscopy a soft and smooth surfaced yellowish tumor mass was observed in the uterine cavity. But no papillary lesions and atypical vessels were seen. Biopsy suggested adenocarcinoma, but frozen section of the tumor gave the impression of malignant Müllerian mixed tumor.

Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done on January 28, 1993. The lymph nodes could not be removed due to extensive adhesion to the pelvic wall probably due to the effect of previous radiation therapy. The patient was discharged from the hospital after full recovery and was advised to take a total 6 course of chemotherapy including cisplatin 120mg/m² in every 4 week period. The patient completed the course and no recurrence has been noticed yet.

Laboratory findings: Her laboratory investigations were insignificant. CA-125 was 240 during admission, 100 pre-operatively, 24 post-operatively and 15 in first follow up.

Microscopic findings: Routine light microscopic examination disclosed proliferation of atypical cells and necrotic tissue. The tumor was composed of both epithelial and mesenchymal components. The epithelial component was

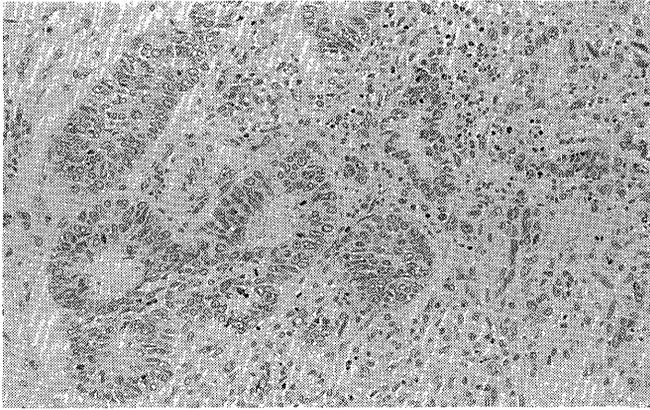


Fig. 1. MMMT showing areas of adenocarcinoma (H.E.x 150).

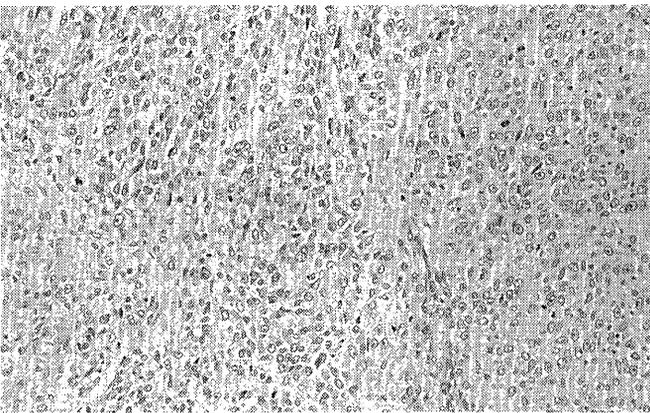


Fig. 2. Undifferentiated sarcoma cells (H.E.x 150).

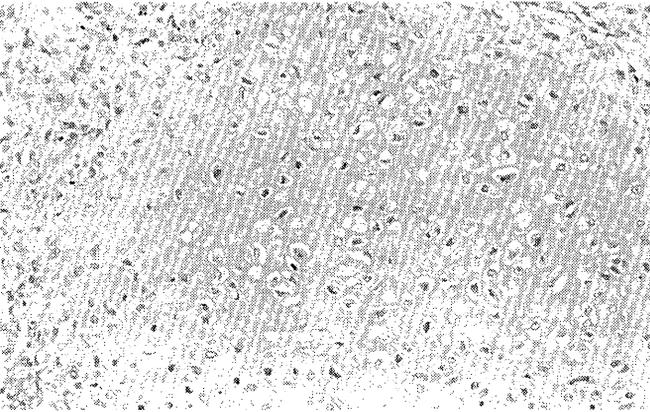


Fig. 3. Chondrosarcoma with giant cells and bizarre nuclei (H.E.x 300).

adenocarcinoma of endometrial type (Fig. 1). The mesenchymal component comprised of both homologous and heterologous elements. The homologous component consisted of undifferentiated spindle-shaped sarcoma cells having irregular nuclei (Fig. 2). The heterologous element comprised of chondrosarcoma with giant cells and bizarre nuclei (Fig. 3). Invasion of malignant cells was noted upto deeper muscle layer, but the adnexae were free from the



Fig. 4. Strong positive reaction for keratin was demonstrated in adenocarcinoma (LSAB x 150).

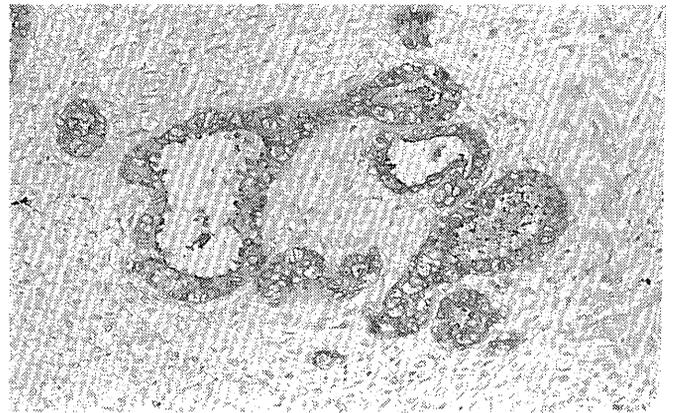


Fig. 5. EMA was also strongly positive in adenocarcinoma (LSAB x 150).

Table 1 Results of immunohistochemistry

	Epithelial component		
	Adenocarcinoma	CHS	UDS
Keratin	+++	-	-
CEA	+++	-	-
EMA	+++	+	+
Vimentin	++	++	+++
Desmin	-	-	-
S-100	+	+++	++
SMA	-	-	-

+++ : Strong positive, ++ : Positive, + : Weak positive, - : Negative, CHS: Chondrosarcoma, UDS: Undifferentiated sarcoma cells.

tumor cells.

Immunohistochemical study: Immunoperoxidase staining was performed by labeled streptavidin-biotin (LSAB) method⁶. Primary antibodies used were keratin, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), desmin, vimentin, smooth muscle actin (SMA) and S-100 protein. Positive results were obtained for keratin, EMA, CEA, vimentin, S-100 and no results were found for desmin and SMA (Table 1). Keratin (Fig.4), EMA (Fig. 5) and CEA showed strong reaction in

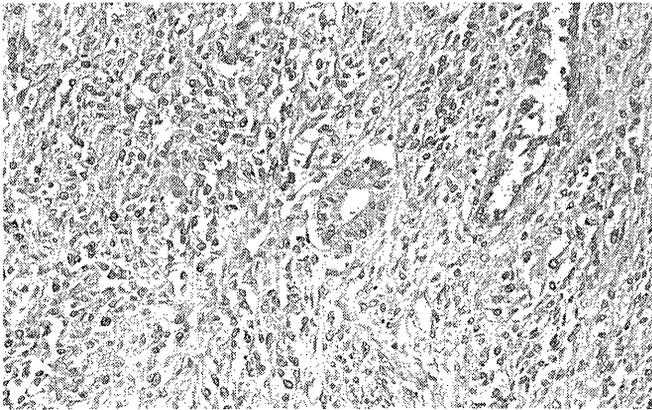


Fig. 6. Immunostaining for vimentin. Undifferentiated sarcoma cells revealed intense reaction and weak positive reaction was noted in adenocarcinoma (LSAB x 150).

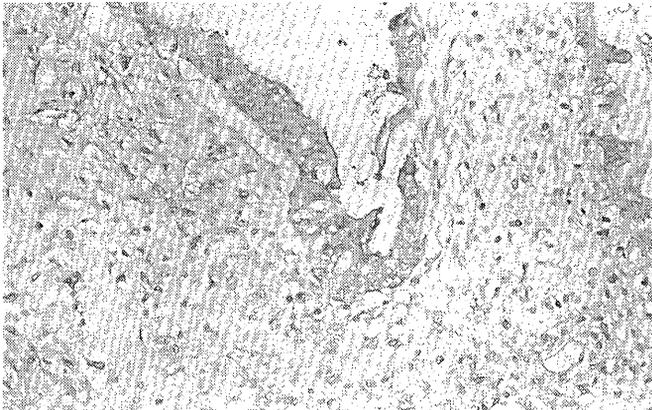


Fig. 7. Immunostaining for S-100 showed weak positive reaction in adenocarcinoma (LSAB x 150).

adenocarcinoma. Adenocarcinoma also presented positive vimentin (Fig. 6) and S-100 (Fig. 7). On the other hand, undifferentiated sarcoma cells and chondrosarcoma elements were strongly positive for vimentin (Fig. 6) and S-100 (Fig. 8), respectively. Undifferentiated sarcoma cells were scatteredly positive for EMA. EMA also showed weak positive result in some area of chondrosarcoma cells (Fig. 9).

Discussion

The most interesting feature of MMT is the presence of both neoplastic epithelial and mesenchymal components. The carcinoma in most cases is an adenocarcinoma (90%) and rarely others. The sarcomatous components may be homologous or heterologous. Homologous sarcoma typically has the appearance of a spindle cell sarcoma, leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, undifferentiated sarcoma, or any combination thereof. The heterologous elements may contain one or more elements normally not present in the uterus. They are

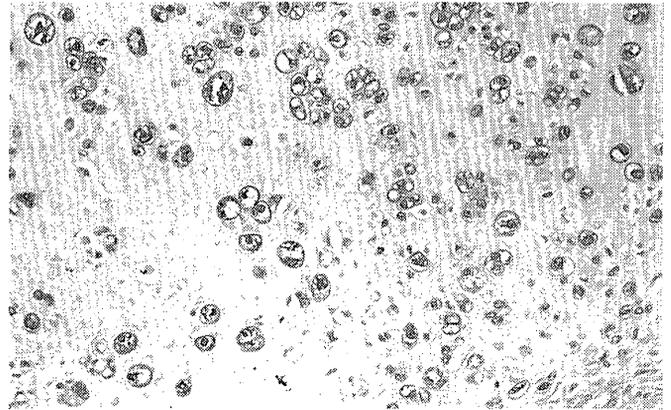


Fig. 8. Strong positive reaction of S-100 protein was demonstrated in chondrosarcoma (LSAB x 150).



Fig. 9. Chondrosarcoma cells showed weak positive reaction for EMA (LSAB x 300).

as follows: rhabdomyoblasts, foci of cartilage or chondrosarcoma, osteoid, bone or osteosarcoma and liposarcoma^{7,8}. In our reported case the epithelial component was composed of adenocarcinoma. Mesenchymal portion of the tumor showed both homologous and heterologous elements. Undifferentiated sarcoma cells were identified as homologous element. Foci of chondrosarcoma with giant cells and bizarre nuclei was the heterologous element of the tumor.

However, as to the histogenesis of MMT developing in the uterine body, it is considered that the tumor arises from the endometrium, which is derived from the Müllerian system embryologically⁹. In addition, the least differentiated cells in the endometrium are regarded as the immediate precursors of uterine MMT.

Epithelial and mesenchymal components can be easily separated by immunostaining. Various studies previously showed that epithelial components are positive for keratin, EMA, CEA. On the other hand, mesenchymal components are usually positive for desmin and vimentin^{11, 12, 10}. Our study also reflected the conventional result. Variations of these results are also observed in different

studies^{10, 18}). In our case, adenocarcinoma cells were not only positive for epithelial markers, but also show weaker reaction for vimentin and S-100. The mesenchymal components, on the other hand, also showed weak positive result for EMA in some area. Desmin and SMA in our case showed negative results in both areas.

Coexpression of keratin and vimentin in sarcoma and carcinoma such as synovial sarcoma, epitheloid sarcoma, ovarian carcinoma, adenocarcinoma of lung and renal cell carcinoma has been reported previously^{14, 15, 16}). S-100 protein was also previously demonstrated in various non-nervous tissues and tumors¹⁷). Like the study of Chung et al.¹⁸) we also identified EMA in some areas of sarcomatous elements. S-100 was strongly positive in areas of chondrosarcoma and also showed positive reaction in adenocarcinoma and undifferentiated sarcoma cells. The immunohistochemical result of the present case was a little bit complex.

However, specific differentiation was much easier in comparison with routine histopathological examination. The expression of intermediate filaments and other molecular markers by tumor cells are sometimes different in comparison with their normal counterpart. Some papers stressed about the modifying role of 'microenvironmental' substances such as hormones, vitamins and others in the expression of these cell markers¹⁹). Eventually such factors may influence regulation of genes of these intermediate filaments and those of other molecular markers. It can be regarded as an explanation of positivity for vimentin and S-100 in carcinoma cells, and for EMA in chondrosarcoma and undifferentiated sarcoma cells. However the complex histogenesis of this tumor needs more elucidation.

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