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CASE REPORT

Malignant Mixed Mullerian Tumor of the Extra-genital Coelomic Epithelium: Report of Two Cases

Irene G IBANEZ-MANLAPAZ,[1] David McCOY,[2] Vincent VINCENT III,[3] and Ulla Jo ULE[4]

[1]Departments of Pathology, [2]Surgery, [3]Obstetrics & Gynecology and [4]Medicine, St. Frances Cabrini Hospital, Alexandria, Louisiana, USA

Malignant mixed mullerian tumors of the extra-genital coelomic epithelium (female peritoneum) are rare. Since the first case report in 1955, only nineteen have been described. In our Case 1 a 58 year-old G3P3 (gravidity = 3; parity = 3) white female with mixed mullerian tumor, homologous type, involving the abdominal peritoneum was treated with surgery and chemotherapy (doxorubicin hydrochloride and cis-platinum). She died of the disease 20 months after initial surgery. Case 2 is a 75 year-old G0P0 (gravidity = 0; parity = 0) white female with mixed mullerian tumor containing heterologous elements involving the pelvic peritoneum who was treated with surgery and chemotherapy (ifosfamide with mesna). She relapsed 6 months after surgery and refused any further treatment. She died 2 weeks later. These cases support the fact that malignant mixed mullerian tumor of the female peritoneum is rare and usually affects elderly females. It has poor prognosis and among the 15 reported cases with follow-up indicating time and presence of disease at death, only 5 survived more than 12 months after initial surgery. (Pathology Oncology Research Vol 3, No 2, 130–134, 1997)

Key words: extra-genital mullerian tumor, carcinosarcoma, poor prognosis, female peritoneum

Introduction

Malignant mixed mullerian tumors are relatively uncommon biphasic neoplasms of the female genital tract occure more frequently in the uterus and ovaries and to a lesser frequency in the fallopian tubes and vagina[1] which compose the primary mullerian system. This is derived from the mullerian duct, an invagination of the coelomic epithelium into the urogenital ridge. The coelomic epithelium also gives rise to the abdominal and pelvic peritoneum, the secondary mullerian system.[2] Malignant mixed mullerian tumor of the female peritoneum is even rarer. Since the first case report in 1955 by Ober & Black,[3] to our knowledge there have been only 19 well documented case reports of extra-genital malignant mixed mullerian tumors in the English literature.[4-18] Six of these cases[7,9,10,14,16,18] were either preceded by or concurrent with neoplasms or disorders involving the primary mullerian system. We report two additional malignant mixed mullerian tumor of the secondary mullerian system, (*Table 1*).

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Correspondence: Irene G IBANEZ-MANLAPAZ, M.D., Department of Pathology, St. Frances Cabrini Hospital, 3330 Masonic Drive, Alexandria, Louisiana 71301, U.S.A.; Tel: (318) 448-6740, fax:-(318) 448-6825

Case reports

Case 1

The patient is a 58-year-old , G3P3, white female who presented with a "bulge" in her left groin which had been gradually increasing in size for approximately 2 months prior to consultation. This was associated with bloating and abdominal cramps. She denied any nausea and vomiting but showed diminished appetite and weight loss of about 10 lbs. She had occasional constipation but otherwise no other bowel problems. Past medical history revealed two cesarian sections. Physical examination revealed a well healed lower abdominal midline scar with easily reducible 5.0x4.0 cm incisional hernia and left inguinal hernia. At the time of incisional hernia repair an omental mass measuring 15.0 cm in diameter, several scattered abdominal peritoneal nodules measuring from 0.5 cm to 1.0 cm and pelvic peritoneal nodules adjacent to the

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Table 1. **Review of Reported Female Peritoneum MMMT in the Literature**

Authors	*Age*	*Parity*	*Diagnosis*	*Site*	*Rx*	*Follow-up*
Ober[3]	74	G0P0	MMMT, HM	Pelvic	Surgery, RT peritoneum	DWD at 5 mo
Ferrie[4]	47	G6PS	MMMT, HM	Abdominal retroperitoneum	Surgery	Unknown
Weiss-C[5]	77	G1P1	MMMT, HT	Cecal peritoneum	Surgery	DWD at 7th day (lung embolus)
Marchevsky[6]	40	G0P0	MMMT, HM	Cul-de-sac peritoneum	Surgery, CT adriamycin (A) cisplatinum (P)	DWD at 12 mo
Herman[7]	72	?	MMMT, HT	Abdominal post./retro peritoneum	Surgery, CT A, Cytoxan (C) DTIC, vincristine	DWD at 6 mo
Hasiuk[8]	77	G0P0	MMMT ,HT	Pelvic/Abdo. peritoneum	Surgical biopsy	DWD at 20th day
Chumas[9]	67	G2P1	MMMT, HM	Rectosigmoid peritoneum	Surgery, CT	DWD at 24 mo
Chen[10]	58	G2P2	MMMT, HM	Pelvic, peritoneum	Surgery, RT	DWD at 73 mo
El-Jabbour[11]	76	G3P3	MMMT, HT	Asc. Colon peritoneum	Surgery	DWD at 2 wk
Fenoglio-P[12]	?	?	MMMT, HT	Cecal peritoneum	Surgery	?
Solis[13] .	54	G0P0	MMMT, HT	Cul-de-sac peritoneum	Surgery	?
Garde[14]	65	G4P3	MMMT, HT	Diaphragm peritoneum	Surgery, CT A,P,Ifosfamide (I)	DWD at 6 mo
Nimaroff[15]	82	G0P0	MMMT,HM	Sigmoid colon peritoneum	Surgery, CT A,P,C	DWD at 24 mo
Garamvoelgyi[16]	60	G0P0	MMMT, HT	Pelvic/abdo peritoneum	Surgery, CT A,P,I	DWD at 24 mo
Garamvoelgyi[16]	64	G2P2	MMMT, HM	Pelvic peritoneum	Surgery, CT Ifosfamide	DWD at 8 mo
Garamvoelgyi[16]	84	G5P5	MMMT, HT	Pelvic peritoneum	Surgery ? liver metastases	Dead at 12 mo
Westra[17]	55	?	MMMT, HM	Spleen peritoneum	Splenectomy	DWD at 9 mo
Mira[18]	62	G3P3	MMMT, HT	Pelvic peritoneum	Surgery, CT Cisplatinum	AWD
Mira[18]	83	?	MMMT, HT	Cecal	Surgery	DWD at 6 mo
Present study						
Case #1	58	G3P3	MMMT, HM	Abdominal peritoneum	Surgery, CT A,P	DWD at 20 mo
Case #2	75	G0P0	MMMT, HT	Pelvic peritoneum	Surgery, CT Ifosfamide	DWD at 6.5 mo

MMMT – Malignant Mixed Mullerian Tumor, HM – homologous, HT – heterologous, RT – radiation therapy, CT – chemotherapy, DWD – dead with disease, AWD – alive with disease, AWOD – alive without disease

right ovary measuring from 2.0 cm to 5.0 cm in diameter were noted and submitted for pathological examination and 1500 cc of hemorrhagic ascitic fluid was obtained. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH with BSO) was also performed. On gross examination the omental mass and peritoneal nodules showed reddish-tan, soft to friable fish-flesh like appearance. The microscopic sections of these tumors revealed poorly differentiated adenocarcinoma while the mesenchymal component disclosed undifferentiated sarco-

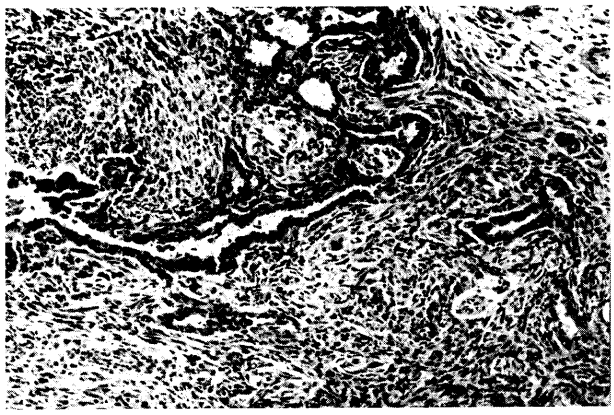

Figure 1. Malignant mixed mullerian tumor, homologous type showing poorly differentiated adenocarcinoma and undifferentiated sarcoma.

ma. *(Fig.1.)*. Immunohistochemical studies using immunoperoxidase technique demonstrated positive reaction of the epithelial cells with antibodies to cytokeratins AEl:AE3 and a negative reaction with S100 protein. The epithelial cells were also focally reactive with antibodies to vimentin and carcinoembryonic antigen. The sarcomatous component reacted positively with antibodies to S100 protein and vimentin and negatively to cytokeratin and CEA. A portion of the omental tumor was submitted to Mayo Medical Laboratories, Rochester, MN for electronmicroscopic studies. The neoplastic cells resembling sarcoma at the light microscopic level were also often spindled ultrastructurally and intracellular junctions appeared focally suggesting metaplastic carcinomatous component rather than a fully differentiated sarcoma. Both fallopian tubes and ovaries showed microscopic foci of similar high grade neoplasms at the peritoneal surface. Endometriosis was seen

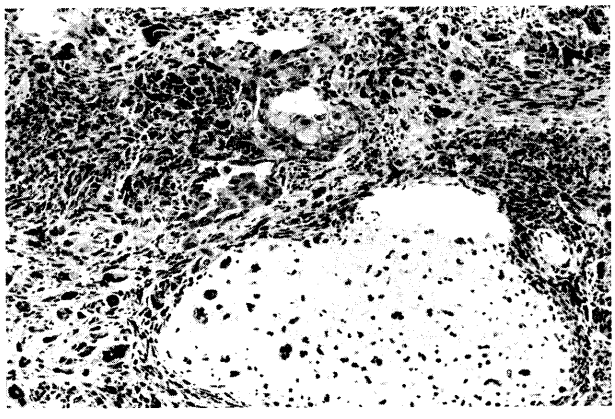

Figure 2. Malignant mixed mullerian tumor, heterologous type, consisting of poorly differentiated adenocarcinoma and undifferentiated sarcoma with focal chondrosarcomatous component.

on both ovaries while the endometrium showed a benign polyp. Post-op cancer antigen 125 (CA-125) was 559 U/mL (ref. range: 0-35 U/mL). The patient received 6 cycles of Adriamycin (85 mg/m2) and cis-platinum (85 mg/m2) and clinically was in remission for 16 months. On follow-up she complained of increasing abdominal discomfort for 3-4 weeks; however, a repeat CT scan was negative. The abdomen was soft, non-tender and a 3.0x3.0 cm easily reducible incisional hernia above the umbilicus and left inguinal hernia were again observed. Patient was scheduled for incisional and inguinal herniorrhaphy and at exploration recurrent tumor nodules measuring from 1.0 to 3.0 cm were noted at the right upper quadrant area just above the hepatic flexure of the colon and below the liver as well as on the left side of the pelvis just lateral to the rectum. Smaller implants were also present around the small intestine. Microscopic studies revealed malignant mixed mullerian tumor, homologous type, similar to the initial neoplasm. She was again placed on Adriamycin and cisplatinum, but experienced fever, ileus, ascites, weakness and severe depression. At this point her condition rapidly declined and she died 20 months after the initial operation. An autopsy was not performed.

Case 2

This is a 75 year-old, G0P0, white female who noted abdominal bloating and swelling several weeks prior to consultation. There was no history of change of bowel habits until 1 week before consultation in which she had constipation, and 5 days later, urinary frequency. She had no pain but only slight abdominal discomfort. Her LMP was in 1974 and she was not on hormone replacement. Past medical history revealed a right hip fracture 2 years previously, during aerobic exercise in which intermedullary screw was placed. On examination a 19.0 cm pelvic mass extending above the symphysis pubis and occupying the entire cul-de-sac was palpated. Uterus was small while the cervix and vagina were normal. Sonogram and CT scan revealed a large complex pelvic mass measuring 18x15 cm. The left ovary was not identified while the right ovary measured 3.1x2.0 cm. Pre-op CA-125 was 725. She underwent exploratory laparotomy and a 23x15 cm pelvic mass was taken out as well as tumor implants around the small bowel measuring from 3.0 to 5.0 cm. TAH with BSO, omentectomy and appendectomy were also performed. Microscopic exam of the tumors showed poorly differentiated adenocarcinoma while the stroma showed undifferentiated sarcoma with focal chondrosarcomatous component. *(Fig.2.)*. The epithelial cells were reactive to cytokeratin (CAM 5.2) while the stromal component was reactive to vimentin. Immunoperoxidase staining for S100 antigen, HCG, actin and desmin were negative. The mesoappendix and omentum were involved by the tumor while the uterus, ovaries

and fallopian tubes did not show any tumor involvement. Post-op she received 6 cycles of Ifosfamide 3.95 g/day x 3 days with Mesna 3.95 g/day x 4 days. Six months after the initial operation, the patient relapsed and refused any further treatment. About two weeks later she died. Autopsy was not performed.

Discussion

Extragenital mixed mullerian tumor is a rare biphasic neoplasm usually occurring in older women. It has a poor prognosis with survival ranging from 7 days to 6 years.[3-8] Malignant mixed mullerian tumors are classified into homologous type in which the stromal component consists of tissue inherent in the location, and heterologous type in which mesenchymal component like chondroid and osteoblastic tissues is not indigenous to the area of the tumor. Malignant mixed mullerian tumor in extragenital sites have been postulated to originate from pre-existing foci of endometriosis,[3] mullerian duct remnants[4] and the secondary mullerian system (female peritoneum)[2] which are all derived from the coelomic epithelium. The endometriotic implants could be benign metaplastic proliferation of the mesothelial cells while malignant mixed mullerian tumors are metaplastic carcinomas of the peritoneal mesothelial cells. The multiple potential capabilities of the peritoneal mesothelium can be observed in its deciduous reaction during ovulation or pregnancy, extragenital serous papillary adenocarcinoma,[19,20] endometrial stromal neoplasms[21] and carcinoma and adenosarcoma.[22] The patient reported by Chumas et al[9] as well as our case #1 which showed endometriosis on both ovaries would support the theory of endometriotic implants transforming into a malignant biphasic neoplasm although the possibility of metaplastic carcinoma arising from the peritoneal mesothelium can not be discounted. Multifocal tumor involvement, instead of the multiple metastases as seen in case #1, would favor the theory of the secondary mullerian system. Case #2 did not show any ovarian or uterine endometriosis or salpingiosis and would also support Lauchlan's theory.[2]

There are several theories postulated as to the histogenesis of extragenital malignant mixed mullerian tumors to explain their biphasic appearance[16]: the "collision" theory (carcinoma and sarcoma occurring simultaneously), "conversion" theory (metaplastic carcinoma) and the "combination" theory in which both the epithelial and stromal components originated from a common stem cell (coelomic derived epithelium). The metaplastic carcinoma and common stem cell theory are not mutually exclusive. Recent ultrastructural and immunohistochemical studies[23,24,25] have shown co-expression of keratin and vimentin markers and metaplastic transformation of malignant epithelial cells which would support both the conversion or combination theories. Masuda et al[26] further proved the conversion or metaplastic theory in their study in which cell lines established from malignant mixed mullerian tumors showed the ability of the epithelial tumor cells to transform into epithelial, mesenchymal or both types of differentiation in vitro, while the mesenchymal cells did not show similar capabilities. The immunohistochemical studies of both cases #1 and #2 and electron microscopic picture of case#1 support the metaplastic carcinoma histogenesis theory.

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