Malignant Mixed Müllerian Tumor in Ascitic Fluid: A Case Report with a Brief Review of Literature

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Citation

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Abstract

Exfoliation of neoplastic cells from the malignant mixed müllerian tumor (MMMT) in peritoneal fluid is rare. Here, we report a case. A 55-year-old, postmenopausal woman presented with abdominal mass and ascites. Cytologic examination of the ascitic fluid sample revealed high cellularity with a bimodal population of cells comprising of adenocarcinoma cells and loose aggregates of degenerated stromal-like cells, morphology of which was somewhat better appreciated in Papanicolaou (PAP) stained smears. Nonetheless, due to the degenerative change that affected the stromal-like cells in particular, a preoperative diagnosis of adenocarcinoma was offered. Histologic examination of the total hysterectomy specimen showed features consistent with malignant mixed müllerian tumor (MMMT) of the uterus. The present case emphasizes the importance of a more careful cytologic examination in rare instances of MMMT presenting with ascites. Examination of PAP stained smears is of particular help in identifying the dual population of MMMT.

INTRODUCTION

Identification of malignant cells in peritoneal washings and ascitic fluid specimens has established prognostic and therapeutic implications in the management of most forms of gynecologic neoplasms.[12]The gynecologic neoplasms commonly manifesting with malignant ascites are mostly the malignant ovarian tumors of the surface epithelial origin, such as papillary serous cystadenocarcinoma.[3] Although rare, cytology of other ovarian malignancies such as germ cell tumors and sex-cord stromal tumors has also been documented.[145]Among uterine malignancies, cytologic aspects of endometrial carcinomas, [6] malignant mixed müllerian tumors (MMMT) [78910]and other uterine sarcomas have been dealt with.

Malignant mixed müllerian tumor (MMMT) is a biphasic, malignant tumor of uterine or ovarian origin, characterized by both carcinomatous and sarcomatous components.[8]It is more common in the uterus; affecting mainly the postmenopausal women.[1] The tumor carries a very poor prognosis, irrespective of the clinical stage, histologic grade, or the type of stroma. Although, the incidence of positive cytology in MMMT is very low; patients presenting with advanced stage and lymphnode and/or ovarian metastasis have been found to have a high percent of positive peritoneal cytology.[8] Significantly, some of the studies have correlated the positive peritoneal cytology with the clinical stage of the disease in cases of MMMT.[71112] This fact stresses the importance of a precise detection of exfoliated neoplastic cells in ascitic fluid/peritoneal washings of such rare cases.

We report a case of MMMT presenting with ascites, describing its cytomorphology and the diagnostic problem, the cytopathologists may encounter.

CASE REPORT

A 55-year-old, postmenopausal woman was admitted with abdominal distension, vaginal bleeding and pelvic pain of one month duration. Abdominal examination revealed ascites and a mass of 20 weeks' size. Pervaginal examination revealed an enlarged, bulky uterus. A 10 ml of hemorrhagic fluid was sent for detection of malignant cells, following which a total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) was done.

Cytologic findings: Ascitic fluid sample was routinely processed by centrifugation technique; air dried smears and, the smears wet fixed in 95% ethanol were stained with May-Grünwald-Giemsa (MGG) and Papanicolaou techniques respectively. With the additional solid sediment particles, cell blocks were made, using the standard plasma-thrombin method. Hematoxylin and eosin stained (H&E) cell block sections were studied.

The smears were highly cellular with cells displaying varying degree of degenerative change. A careful observation revealed two distinct populations of cells comprising of somewhat better preserved, and easily identifiable clusters of epithelial cells; along with more strikingly degenerated aggregates of stromal-like cells which were initially mistaken for inflammatory cell aggregates. Some of the stromal aggregates revealed structures resembling calcified material (Figure-1A). The epithelial component was seen as compact clusters (Figure-1B); rare epithelial cells were seen dissociated. Their morphology was better appreciated in the Papanicolaou stained smears, in which they exhibited moderate to marked pleomorphism; high N: C ratio; vesicular to hyperchromatic nuclei; prominent nucleoli; nuclear overcrowding; along with moderate to abundant, vacuolated cytoplasm and indistinct cell borders. Some of these epithelial clusters showed glandular and papillary architecture (Figure-2A). The stromal-like cells chiefly formed loose aggregates with large numbers of dissociated cells. A careful examination of these cells showed mild to moderately pleomorphic, round to-ovoid to- polygonal cells having distorted nuclei and vacuolated cytoplasm with indistinct cell borders. Mitosis-like structures were identified. In Papanicolaou stained smears oval to spindly stromal-like cells, having hyperchromatic to pyknotic nuclei could be better appreciated (Figure-2B). Overall, the degenerative change was more striking in the stromal-like component than in the epithelial cells. As it was difficult to comment upon the stromal-like cells, based only on the clearly identifiable malignant epithelial cells, a diagnosis of adenocarcinoma was offered. The adenocarcinoma cells were picked up easily on cell block sections. However, degenerated cellular components were not commented upon.

Figure 1

Figure 1: A. MMMT showing tiny calcific structures enmeshed in a poorly preserved endometrial stromal fragment; background shows degenerated inflammatory cells and macrophages (MGG stain;x400); B. shows an adenocarcinomatous cluster of MMMT having a smooth contour, seen in close association with a degenerated stromal fragment (MGGx400)

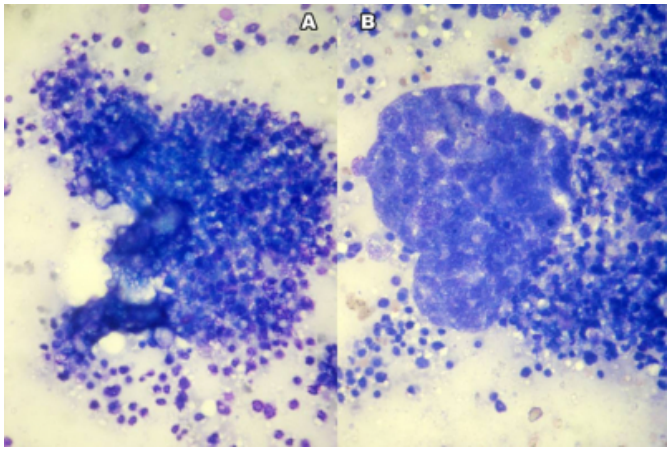
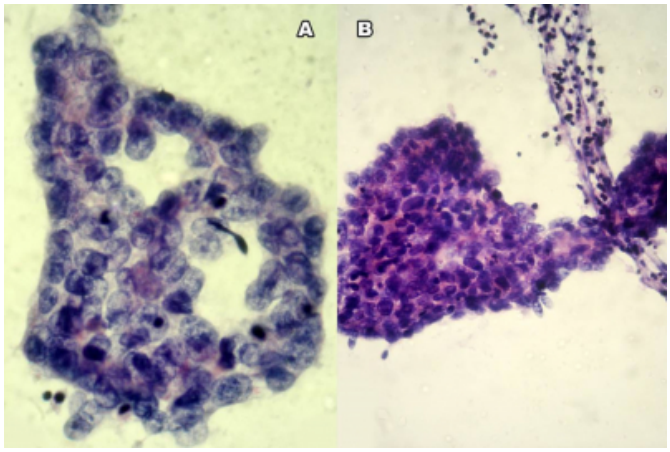


Figure 2

Figure 2: A. MMMT showing a cluster of adenocarcinoma with glandular pattern with cells displaying high N: C ratio, vesicular nuclei, prominent nucleoli and scanty to moderate cytoplasm (Papanicolaou stain x 400); B. A poorly differentiated, pleomorphic, malignant cell cluster with an adherent fibrovascular strand; the malignant cells exhibit round to oval to spindly morphology suggesting their stromal nature (Papanicolaou stain; x400)



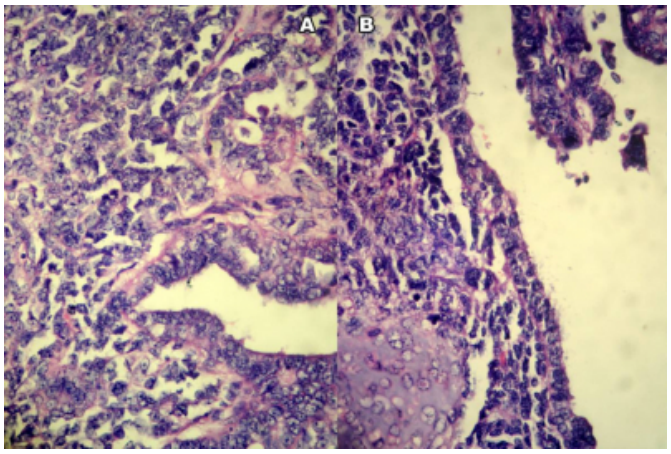
Histopathologic findings: The uterus and cervix measured14x10x8cm. The specimen was already cut open with a necrotic mass protruding exteriorly. The growth was polypoid and attached to the uterine wall at posterior and fundal aspects. The cut surface of the growth was solid, gray-white to gray-brown with necrotic areas, seen infiltrating the myometrium. The right tube was replaced by

a gray-white, nodular growth. The right ovary was 3.5x3x2cm in dimension, with nodular external surface and a grayish white cut surface. A serosal nodule of 0.3mm was seen adjacent to the right ovary on the uterine surface, cut surface of which was gray white. The left tube and the ovary were unremarkable. Also received was a flap of omentum measuring 5x3x1cm, which showed a gray white nodule measuring 1.5cm in diameter.

Microscopic examination of the representative areas showed features consistent with malignant mixed müllerian tumor, with the epithelial component showing features of poorly differentiated adenocarcinoma and the sarcomatous component composed of polygonal to spindle cells (Figure-3A), and large pleomorphic tumor giant cells exhibiting acidophilic cytoplasm. Also seen was a focus of immature cartilage (Figure-3B). The tumor was seen invading the cervix and uterine myometrium, extending onto the serosal surface. The right adnexae and omentum showed metastatic deposits without any mesenchymal elements . The parametria and the left adnexal structures were free from the tumor.

Figure 3

Figure3: A. MMMT showing a poorly differentiated adenocarcinomatous area (H&E Stain, X4000); B. glandular and spindle cell elements of MMMT, along with a focus of immature cartilage (H&E stain, X400)



DISCUSSION

We have reported a case of MMMT in ascitic fluid sample. It is an uncommon malignant uterine tumor, known to be associated with poor prognosis.A positive peritoneal cytology of MMMT has been observed mainly in patients presenting with advanced stage of the disease. Of the prognostic indicators of this tumor; the mitotic index (MIBL1) and p53 expression are considered highly significant, with mitotic indices averages of carcinomatous component, generally being higher than those in the sarcomatous areas.[8]

Significant numbers of studies have elaborated on the cytomorphologic aspects of this rare gynecologic malignancy. [7,8,9,10]Going through the cytology literature, one can understand the variation in the cytologic manifestation of these tumors in ascitic fluid and peritoneal washing specimens. Kanbour et al [7] studied 28 fluid samples from 54 patients with MMMT of which 10 were ascitic fluids and 18 were peritoneal washings. It was noted that ascitic fluids contained more malignant cells than the peritoneal washings. These cells exhibited varied degree of cytoplasmic vacuolation, enlarged nuclei with anisokaryosis, irregular shape and abnormal chromatin patterns and prominent nucleoli. The adenocarcinomatous component displayed no features that would distinguish them from other intraperitoneal adenocarcinomas. When sarcomatous component was present, it was seen as isolated cells, or loose aggregates. The cells were elongated or caudate with cyanophilic cytoplasm, suggesting connective tissue or muscle origin. Endometrial stromal sarcoma cells were small, round, or spindle shaped with scanty, wispy, cyanophilic cytoplasm (comet cells). These small malignant cells often had tapering cytoplasm, incompletely surrounding their nuclei. Occasionally, tissue fragments containing blood vessels surrounded by neoplastic endometrial stromal cells were seen.[7] Wang et al [10] reviewed 102 cases of uterine sarcomas and reported 3 abnormal cervical smears and 2 abnormal peritoneal fluids from 2 cases of MMMT and a case each of leiomyosarcoma and high grade stromal sarcoma. They emphasized on the diagnostic difficulty encountered in their cases mainly due to the rarity of such occurrences. Although detection rate of malignancy was high (90%), the majority of malignant cells in their cases originated from the adenocarcinomatous component. Nonetheless, cytopathologists should keep the diagnosis of uterine sarcoma in mind, when abnormal cells with unusual findings are encountered in peritoneal cytology.[10]Kalogeraki et al [8] in their single case report of MMMT reported cellular ascitic fluid smears consisting of reactive mesothelial cells, mature lymphocytes, few histiocytes and epithelial and nonepithelial components in a necrotic background. The epithelial component was dissociated; the cells exhibited small round nuclei, abundant cytoplasm with no pleomorphism. The nonepithelial component consisted of round, undifferentiated cells with no pleomorphism or mitotic activity. Immunocytochemically, epithelial cells were BerEp4 and CD-15 positive; while the

nonepithelial components expressed desmin .[8]Modzelewski Jr [9] reviewed 50 peritoneal effusions from 38 patients, of which 16(42%) had positive effusion cytology; 13 cases were diagnosed as adenocarcinoma and 3 cases (19%) were found to have sarcomatous component. Significantly, IHC performed on 8 of these cases did not alter the original diagnosis. The cytomorphologic features found to be helpful in the recognition of sarcomatous component included a dissociated smear pattern of pleomorphic round to oval cells and/or spindle cells. They concluded that IHC was not of much use in unsuspected cases of MMMT, unless the cytology was suspicious.[9]

Our case of MMMT was diagnosed as adenocarcinoma; the poorly preserved loose aggregates of stromal cells were not commented upon. Even in the cell block material, we could pick up only the adenocarcinoma component with certainty. Both in the cytologic smears and cell block sections, the adenocarcinoma component displayed features similar to those of any other intraperitoneal adenocarcinomatous deposits. In contrast to the dissociated adenocarcinoma cells reported by Kalogeraki et al, [8] the epithelial component in our case appeared cohesive with smooth borders; some clusters exhibited glandular and papillary pattern. Following histopathologic diagnosis, the review of cytologic smears revealed at least, occasional, somewhat better preserved stromal elements in the Papanicolaou stained cytologic smears (figure2B), emphasizing the need for a more critical cytologic evaluation.

A few studies have dealt with the prognostic significance of positive peritoneal cytology in MMMT.[7,11,12]Kanbour et al [7] correlated peritoneal fluid cytologic findings with stage of the disease. They observed that the positive cytology directly correlated with the depth of invasion of MMMT. The extent of disease as measured by clinical stage is being considered the most important prognostic factor. In addition to this, these authors identified cytology of peritoneal fluids and washings, as another important prognostic factor. They found that in stage-I disease, the peritoneal cytology was more predictive of outcome in stage I disease than is the depth of invasion. The greater importance of positive peritoneal cytology over the depth of myometrial invasion was demonstrated in one of their patients with sarcoma in a polyp, which showed no myometrial invasion.[6] Other authors like Lotocki et al [11] and Geszler et al [12] have also reported positive peritoneal cytology in patients with tumor limited to the uterus, to be predictive of early intraperitoneal dissemination and indicative of prognosis, similar to that in patients with advanced stages of the disease. All these studies emphasized the importance of cytologic examination of ascitic fluid, or peritoneal washings at the time of surgery. Although, the present case manifested with an apparently advanced clinical stage; and therefore, a precise diagnosis was of little clinical significance; it is always desirable for a cytopathologist to be aware of the cytomorphologic variations of MMMT in ascitic fluid/peritoneal fluid sample.

In conclusion, Exfoliation of MMMT cells in ascitic fluid is a rare event of clinical significance. In the present case, neoplastic cells in ascitic fluid sample were interpreted as adenocarcinomatous deposits, as degenerative change involving predominantely the stromal cells in particular, made us ignore the mesenchymal element of the tumor. Despite this, we strongly believe that a more careful cytologic evaluation could have helped us in the precise identification of the dual components of MMMT.

CORRESPONDENCE TO

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