Case Reports

Uterine müllerian adenosarcoma with sarcomatous overgrowth and lung metastasis in a 25-year-old woman

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Summary

Uterine müllerian adenosarcoma with sarcomatous overgrowth (MASO), uncommon in premenopausal women, is a rare variant of uterine adenosarcomas characterized by a sarcomatous portion constituting >25% of the tumor. Uterine MASO often appears as a benign, protruding cervical polyp. However, in contrast to typical müllerian adenosarcomas (MAs), MASO is a highly aggressive tumor, frequently associated with a fatal outcome. Though very rare in premenopausal women, because of the high aggressiveness and malignant potential, uterine MASO should be considered, even in women of a young age with benign-appearing polypoid masses, and treated aggressively at the time of initial diagnosis without delay. We present herein a case of uterine MASO in a 25-year-old woman with lung metastasis who was lost to follow-up for one month after the initial diagnosis had been established.

Key words: Uterus; Adenosarcoma; Sarcomatous overgrowth.

Introduction

An aggressive variant of adenosarcoma, müllerian adenosarcoma with sarcomatous overgrowth (MASO) has a benign glandular component and a malignant sarcomatous component that constitutes > 25% of the tumor [1]. It is unusual to diagnose MASO in the premenopausal age group and the most common presenting symptom is abnormal vaginal bleeding, and these tumors are often considered benign [1].

MASO has more malignant characteristics than classic adenosarcoma, and is frequently associated with postoperative recurrence or metastasis with a fatal outcome [1-4]. Because of the rarity of such tumors in the young age group, the clinical suspicion for MASO is very low, often resulting in a delay in diagnosis. Clinicians and pathologists should keep in mind the possibility and characteristics of this gynecologic malignancy.

We present herein a case of uterine MASO in a 25-year-old woman with lung metastasis who was lost to follow-up for one month after the initial diagnosis had been established.

Case Report

A 25-year-old previously healthy nulligravida presented with two months of irregular vaginal bleeding at a local clinic. The medical and surgical histories were unremarkable. On pelvic examination, a 3 cm polypoid mass with a stalk was seen within the cervical os; on ultrasound, a 2.8 x 2.0 x 1.5 cm hypoechogenic endometrial polypoid mass was demonstrated. The patient underwent a hysteroscopic polypectomy with dilation and curettage. The pathologic evaluation confirmed uterine MASO. It was recommended that she be transferred to our hospital for treatment. The initial pelvic magnetic resonance imaging (MRI) showed a 1.6 x 1.4 x 1.1 cm irregular mass within the endometrial cavity that invaded into approximately one-half of the myometrium. There was no abnormal hypermetabolic lesion except for uterus in PET computed tomography (CT). She declined the recommended surgery at that time. She sought evaluation at our hospital again with aggravated vaginal bleeding and abdominal distention after a one month loss to follow-up. Pelvic (MRI) showed a 4.3 x 2.8 x 1.7 cm enlarged mass invading > 2/3 of the myometrium (Figure 1). PET CT and chest CT demonstrated metastases to the left hilar (2 cm) and infrahilar (1.5 cm) lymph nodes and both lungs.

She underwent debulking surgery consisting of a laparoscopic-assisted vaginal hysterectomy, bilateral salpingectomy, pelvic lymph node dissection, paraaortic lymph node dissection, partial omentectomy, and incidental appendectomy. Both ovaries were grossly normal in appearance, thus the ovaries were preserved. As the resectability of the lung metastases was thought not to be technically feasible, the lung masses were left *in situ*. A meticulous survey of the gastrointestinal tract, paracolic gutters, liver, spleen, kidneys, and the undersurface of the diaphragm revealed no additional lesions.

Grossly, the cut surface of the uterine body showed a yellow to brownish mass with focal necrotic area, measuring 5 x 6 cm in size (Figure 2). Microscopically, the endometrium showed protruding biphasic tumor tissue consisting of benign epithelial cells and neoplastic stromal components constituting > 25% of the tumor. The epithelial component was comprised of well differentiated neoplastic epithelial cells. The stromal component showed round or polygonal shaped atypical cells with prominent nucleoli and mitosis (Figures 3 and 4). The tumor tissue infiltrated > 1/2 of the myometrium without penetration of the parametrium. The other pelvic organs and lymph nodes were free of lesions and the washing cytology was negative. The FIGO stage was IVb. Immunohistochemical stains demonstrated that the epithelial cells lining the glands were positive for cytokeratin. The cytoplasm of the stromal cells had a positive reaction for vimentin and p53, but negative for cytokeratin and desmin.

After surgery, the patient received six cycles of combination chemotherapy (intravenous taxol [175 mg/m^2] and carboplatin

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Fig. 1

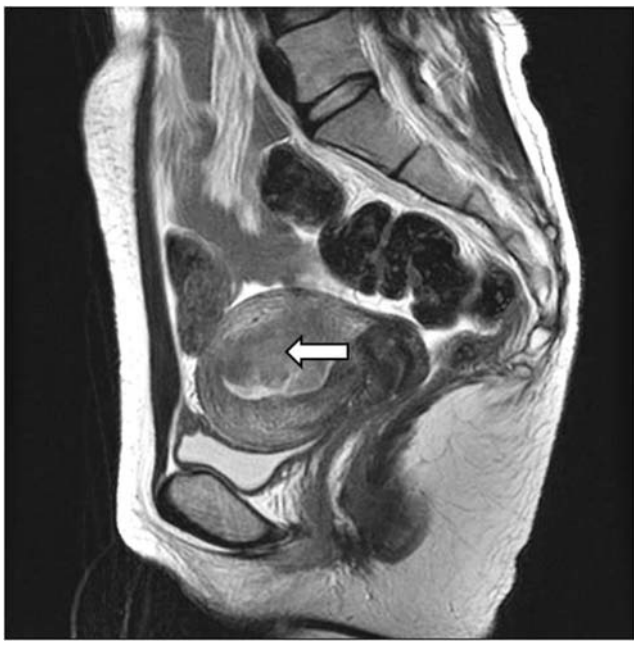

Fig. 2

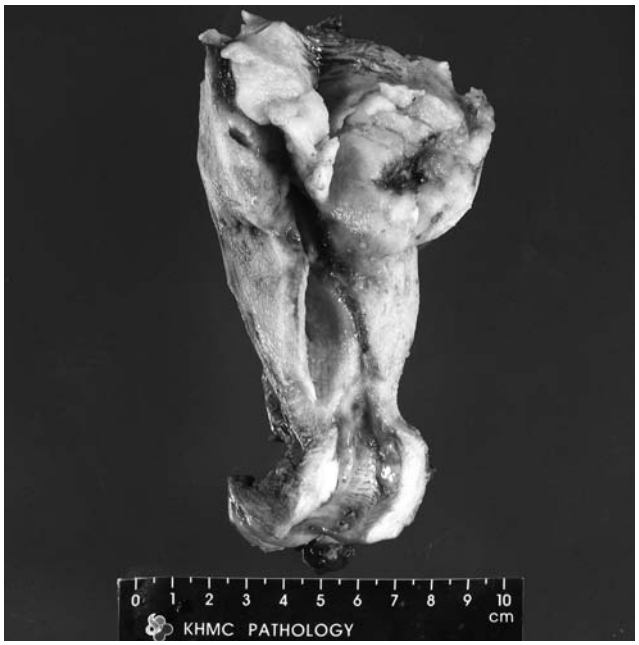

Fig. 3

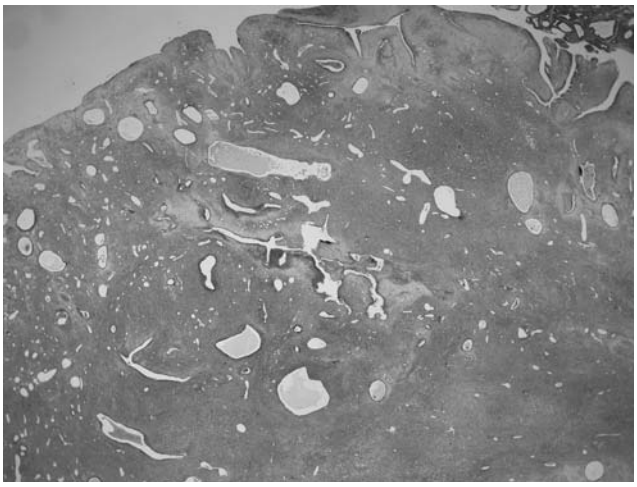

Fig. 4

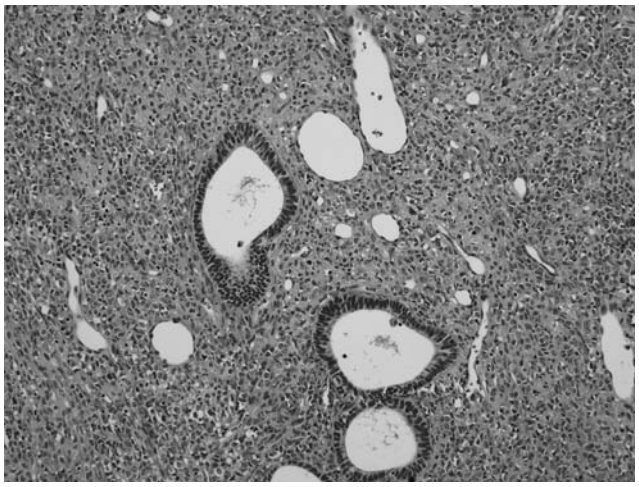

Figure 1. — Pelvic MRI, 4.3 x 2.8 x 1.7 cm, enlarged, irregular, ulcerative surfaced mass invading > 2/3 of the myometrium.
Figure 2. — The cut surface of the uterine body showed a yellow to brownish mass with focal necrotic area, measuring 5 x 6 cm in size.
Figure 3. — The protruding mass shows biphasic tumor composed of a malignant stromal component admixed with an irregular branching benign epithelial component (hematoxylin-eosin, original magnification, X 12.5).
Figure 4. — The tumor shows periglandular sarcomatous overgrowth of round or polygonal atypical cells with mitosis (hematoxylin-eosin, original magnification, X 200).

[AUC 5]). After three cycles of chemotherapy, the chest CT showed improvement of the lung and left hilar lymph node metastases. With completion of six cycles of combination chemotherapy, aggravation of the left hilar left node metastases was seen on chest CT; however, no evidence of recurrent tumor or metastasis on pelvic CT was noted.

She was subsequently treated with second-line combination chemotherapy (6 cycles of intaravenous ifosfamide [1500 mg/m^2] and carboplatin [AUC 5]) and radiotherapy (200 cGY/day [total 6000 cGY]) to the right hilar area for three months. Decreased metastatic involvement to the left hilar lymph nodes and no evidence of lung metastasis were seen following systemic chemotherapy and mediastinal radiotherapy. One month later, however, metastasis to the mediastinal and left supraclavicular lymph node was noted on chest CT and PET CT. The disease progressed rapidly and metastasized to the right proximal humerus and left proximal femur. Five months after the last treatment, her cause of death was the disseminated disease.

Discussion

The spectrum of mixed müllerian tumors ranges from adenofibromas (with benign epithelial and stromal components) and adenosarcomas (with benign epithelial components and malignant stromal components) to carci-

nosarcoma (both epithelial and stromal components are malignant). MASO has a benign glandular component and a malignant sarcomatous component that constitutes more than 25% of the tumor [5].

MASO is a rare variant of adenosarcomas, first described in 1989 [1] and generally originates from the uterine corpus. Krivak *et al*. [2] reported that MASOs were found in 18% (11/60) of MAs between 1988 and 1998, whereas Gallado *et al*. [3] reported a prevalence of 33% (18/37) between 1986 and 2006.

In the series reported by Clement [1] and Clement and Scully [6], the median age of patients diagnosed with MASO was 59 years, with a range of 32-82 years, while the median age of patients diagnosed with MA was 62 years, with a range of 14-82 years. Tumors with sarcomatous overgrowth, as compared with those without sarcomatous overgrowth, occurred in younger women (mean age, 51.5 years vs 65.3 years, respectively), were larger (mean diameter, 10.3 cm vs 4.6 cm, respectively), and were more likely to have heterologous elements (50% vs 0%, respectively) [7].

The most common presenting symptom is abnormal vaginal bleeding (71% of patients) [1], followed by a pelvic mass (37% of patients), uterine polyps (22% of patients), or an enlarged uterus (22% patients), which is morphologically considered to be a benign type.

Based on immunohistological stains of the case described herein, the epithelial cells lining the glands were positive for cytokeratin. The stromal tumor cells were positive for vimentin and p53, but negative for cytokeratin and desmin. These findings were nearly identical to those of other cases, and MASO often shows strong immunoreactions for Ki-67 and p53, and loss of CD10 and PR immunostaining [3, 8].

MA is thought to have a lower malignant potential than other malignant MMMTs. However, MASO has more malignant characteristics than classic adenosarcomas [1, 4]. In uterine MASO, myometrial invasion was noted in 60% of cases (in contrast, < 25% of cases of adenosarcomas without sarcomatous overgrowth) and extension to the serosal surface occurred in 30% of cases (in contrast, < 5% of adenosarcomas without sarcomatous overgrowth) [1, 4]. The recurrence rate was 70%, and 60% of patients died due to tumor progression [1]. Krivak *et al*. [2] reported recurrences of MASO in nine of 11 patients in all stages. Nine of the 11 patients died of recurrent or progressive disease and three patients died within one month. The median survival was 13 months. In four Stage IV cases, patients were treated with surgery followed by combination cisplatin and ifosfamide or single-agent doxorubicin. All patients had recurrences involving the lung and other sites, and died within an average of six months.

In view of the highly malignant potential of MASOs, these patients must be managed aggressively. Due to the rarity of adenosarcomas, there is no consensus regarding adjuvant therapy. Previous treatments included surgery consisting of total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node sampling, and tumor debulking. Additional and adjuvant therapy has included radiation therapy and chemotherapy. If distant metastatic disease is encountered, the patients should be offered systemic chemotherapy. The chemotherapeutic agents consist of either doxorubicin or a combination of cisplatin and ifosfamide with mesna [2]. Recently, Toyoshima *et al*. [9] reported that a combination of paclitaxel and carboplatin for treatment of advanced uterine MMMTs resulted in a complete response rate of 80% and a median progression-free interval of 18 months. Considering the results of our case with refractory pulmonary metastasis and no pelvic recurrence, surgical debulking including respectable metastatic lesion at the initial treatment followed by combination chemotherapy or chemoradiation could have led to a more favorable outcome although there are no substantial recommendations for adjuvant treatment. However, studies addressing the optimal time to initiate postoperative adjuvant therapy in relation to the interval to tumor recurrence are needed to establish recommendations regarding the timeliness of adjuvant therapy and its effect on survival, tumor progression, and the disease-free period [10].

In conclusion, the patient presented herein was an extremely rare case, and one of the youngest patients diagnosed with MASO and distant metastasis and fatal progression. Because MASO of the uterus has a highly aggressive malignant potential, gynecologists and pathologists should be aware of the consequences associated with a delay in the diagnosis and/or initiation of therapy for MASO. And, this entity, although rare, should be in the differential diagnosis of young women presenting with abnormal menstrual bleeding in the presence of a pelvic mass.

References

[1] Clement P.B.: "Mullerian adenosarcomas of the uterus with sarcomatous overgrowth. A clinicopathological analysis of 10 cases." *Am. J. Surg. Pathol*., 1989, *13*, 28.

[2] Krivak T.C., Seidman J.D., McBroom J.W., MacKoul P.J., Aye L.M., Rose G.S.: "Uterine adenosarcoma with sarcomatous overgrowth versus uterine carcinosarcoma: comparison of treatment and survival". *Gynecol. Oncol*., 2001, *83*, 89.

[3] Gallardo A., Prat J.: "Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma". *Am. J. Surg. Pathol*., 2009, *33*, 278.

[4] Hallak M., Peipert J.F., Heller P.B., Sedlacek T.V., Schauer G.M.: "Mullerian adenosarcoma of the uterus with sarcomatous overgrowth". *J. Surg. Oncol*., 1992, *51*, 68.

[5] Arici D.S., Aker H., Yildiz E., Tasyurt A.: "Mullerian adenosarcoma of the uterus associated with tamoxifen therapy". *Arch. Gynecol. Obstet*., 2000, *264*, 105.

[6] Clement P.B., Scully R.E.: "Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature". *Hum. Pathol*., 1990, *21*, 363.

[7] Seidman J.D., Wasserman C.S., Aye L. M., MacKoul P. J., O'Leary T.J.: "Cluster of uterine mullerian adenosarcoma in the Washington, DC metropolitan area with high incidence of sarcomatous overgrowth". *Am. J. Surg. Pathol*., 1999, *23*, 809.

[8] Nagai Y., Kishimoto T., Kato K., Ozaki D., Kondo F., Kobayashi A. *et al*.: "Uterine adenosarcoma with sarcomatous overgrowth: a case report with cytology of overgrown poorly differentiated sarcoma and immunohistochemical identification of epithelial microinvasion". *Int. J. Gynecol. Cancer*, 2002, *12*, 501.

[9] Toyoshima M., Akahira J., Matsunaga G., Niikura H., Ito K., Yaegashi N. *et al*.: "Clinical experience with combination paclitaxel and carboplatin therapy for advanced or recurrent carcinosarcoma of the uterus". *Gynecol. Oncol*., 2004, *94*, 774.
[10] Farhat M.H., Hobeika E.M., Moumneh G., Nassar A.H.: "Uterine mullerian adenosarcoma with sarcomatous overgrowth fatal recurrence within two weeks of diagnosis: a case report". *J. Med. Case Reports*., 2007, *1*, 103.

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