Mullerian adenosarcoma with sarcomatous overgrowth in a premenopausal patient*

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ABSTRACT

We report a case of a 33-years old, nulligravid, diagnosed with mullerian adenosarcoma with sarcomatous overgrowth (MASO), who presented with vaginal bleeding and recurrent endometrial polyp. MASO is a rare type of uterine sarcomas, it is a variant of adenosarcomas with poor prognosis[1].

The index patient underwent primary surgical management with lymphadenectomy with a final stage of IC. Histologic diagnosis was Mulllerian adenosarcoma with sarcomatous overgrowth. A panel of immunostaining for estrogen receptors, progesterone receptors and CD 10 showed diffused positivity for the hormones with loss of CD 10 which is consistent with MASO .

The rarity of MASO has a distinctive histologic features which merits meticulous sectioning as the clinical course and management vary. It has a poor prognosis due to its short and fast course of the disease.

Keywords: Mulllerian adenosarcoma with sarcomatous overgrowth, uterine sarcoma

INTRODUCTION

Uterine sarcomas are relatively rare tumors that account for approximately 1-3% of female genital tract malignancies and between 4-9% of uterine cancers[2,3]. The latest FIGO classification and staging system reflects the different biologic behaviors of the uterine sarcomas, such that leiomyosarcoma has its own staging system, carcinosarcoma is staged similarly to endometrial carcinoma, and endometrial stromal sarcoma and adenosarcomas share the same staging classification.

Mullerian adenosarcoma with sarcomatous overgrowth (MASO) is a variant of adenosarcoma which was first described by Clement et al. as early as 1974[1,3]. It is depicted by growth of a second pure high-grade sarcoma occupying at least 25% or more of the total tumor volume[2,4]. It is correlated with deeper myometrial involvement and poorer prognosis[1-2]. MASO is more common in postmenopausal women and rarely in young reproductive age group which typically presents with vaginal bleeding as the most common symptom[1-4].

We report a case of a 33-year-old, nulligravid, presented with vaginal bleeding, and recurrent endometrial polyp. This case is presented due to the paucity of the cases being reported both locally and international publication. With a high index of suspicion, malignancy should always be ruled out in cases with recurrent endometrial polyp. This can be an effect of unopposed estrogen which can be the primary predisposing factor in development of the MASO. It has a poor prognosis as compared to adenosarcoma. It is associated with post-operative recurrence, metastases, even when diagnosed in early stage[3]. Hence, delayed diagnosis and treatment will have fatal outcomes. Although, there is still no standard treatment but early and accurate diagnosis is imperative for all diseases.

CASE REPORT

A 33-year-old, nulliparous, diabetic woman with primary infertility, who presented with menorrhagia three years ago. She underwent dilatation and curettage which showed an endometrial polyp but was lost to follow-up. A year prior to admission, she had vaginal bleeding and subsequently underwent vaginal myomectomy with endometrial curettage. Histopathology was consistent with myoma uteri and endometrial hyperplasia with atypia in an endometrial polyp. She was given medroxyprogesterone acetate 10 mg per tablet on days 16-25 of menses for three consecutive months however no post-treatment biopsy was performed. She was asymptomatic until a year prior to admission, she again presented with prolonged vaginal bleeding. Endometrial biopsy revealed carcinosarcoma and endometrial polyp. She was advised to undergo hysterectomy, however no consent and was lost to follow-up for five months. Pelvic examination five months after she was lost to follow-up showed a 10 x 10 cm necrotic

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and friable mass prolapsing in the vaginal canal (Figure 1). The cervix was difficult to delineate because of the large vaginal mass. The uterine corpus was enlarged to 18-20 weeks size, with no palpable adnexal masses nor tenderness. The rectovaginal septum was smooth and bilateral parametria were smooth and pliable. Transvaginal ultrasound showed endometrial mass consistent with malignancy with almost full thickness myometrial invasion with endocervical extension (Figure 2).

The patient underwent extrafascial hysterectomy with bilateral salpingooophorectomy and lymphadenectomy. The distal third of the left ureter was inadvertently transected due to the bulky cervix. Left ureteroneostomy, cystorrhapy and stent insertion was performed. Intraoperatively, the uterine corpus measured 11.0 x 9.5 x 5.0 cm and cervix was dilated to approximately 10.0 x 10.0 cm and occupied the pelvis (Figure 3a). On cut section, occupying the entire endometrial cavity was a necrotic and friable mass measuring 14.0 x 9.0 x 4.0 cm with more than 50 percent myometrial invasion (Figure 3b). The mass involved the entire endocervical canal with more than one third cervical stromal invasion (Figure 3c). The vaginal cuff was grossly free of tumor (Figure 3c). The right ovary measured 3.0 x 2.0 x 1.0 cm, with a 1.0 x 1.0 cm solid surface implant which was suspicious for malignancy (Figure 3d). The contralateral adnexa was normal. The intra-operative stage was stage IIA.

Post-operative ureterogram showed smooth retrograde flow of dye from ureteral orifice to the tip of the ureteral stent with no extravasation (Figure 4a). Cystogram revealed smooth bladder wall contour and likewise no extravasation of dye (Figure 4b). On the eight

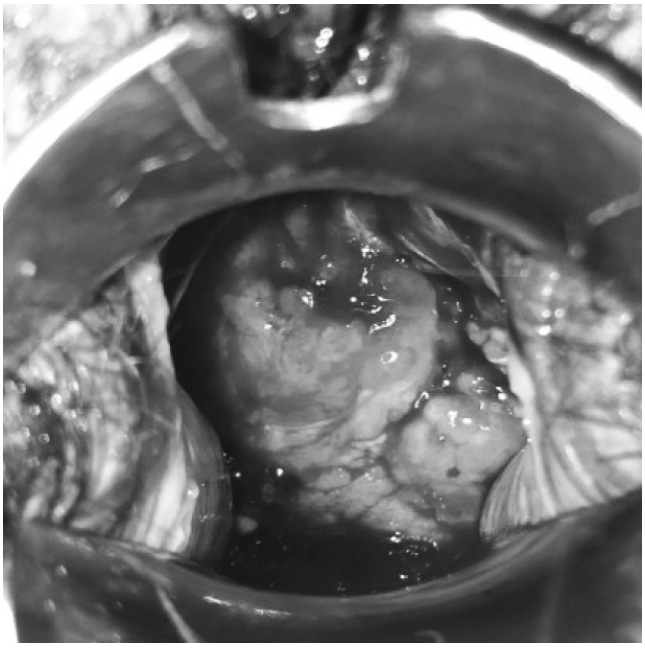

Figure 1. A prolapsing friable, necrotic mass occupying the vaginal canal measuring 10.0 x 10.0 cm

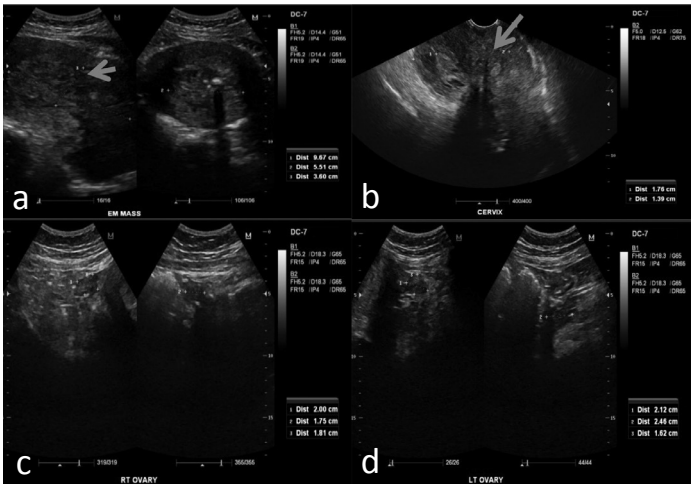

Figure 2. a. A heterogenous mass occupying the entire endometrial cavity (red arrow) measuring 9.7 x 5.5 x 3.6 cm that extends from the fundus down to endocervix with almost full thickness involvement of the posterior myometrium. **b.** A irregular heterogenous mass (red arrow) occupying the endocervical canal measuring 6.1 x 4.7 x 4.9 cm is contiguous from the endometrial mass. **c.** The right ovary is normal. **b.** The left ovary is normal.

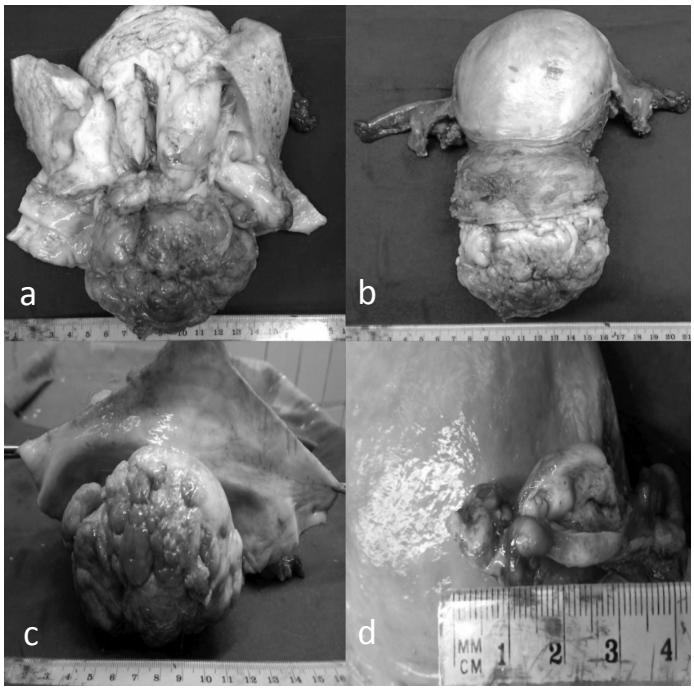

Figure 3. a. Anterior uterus: The uterus measured 11.0 x 9.5 x 5.0 cm, with smooth tan serosal surface. **b.** On cut section, the entire endometrial canal was a necrotic and friable mass measuring of 14.0 x 9.0 x 4.0 cm, with more than 50% myometrial invasion **c.** The mass extended up to the entire endocervical canal with more than 1/3 cervical stromal involvement with 5.0 cm vaginal cuff circumferentially, which was grossly free of tumor. **d.** The right ovary measured 3.0 x 2.0 x 1.0 cm, there was a 1.0 x 1.0 cm solid implant which was suspicious for malignancy.

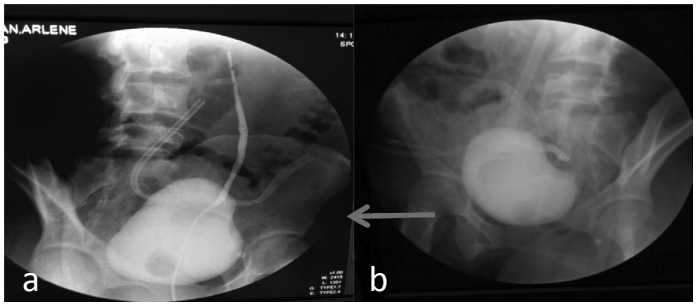

Figure 4. a. URETEROGRAM: Smooth retrograde flow of dye from the ureteral orifice to the tip of the ureteral stent with no extravasation of dye (red arrow). **b. CYSTOGRAM:** Smooth bladder wall contour with no extravasation of dye.

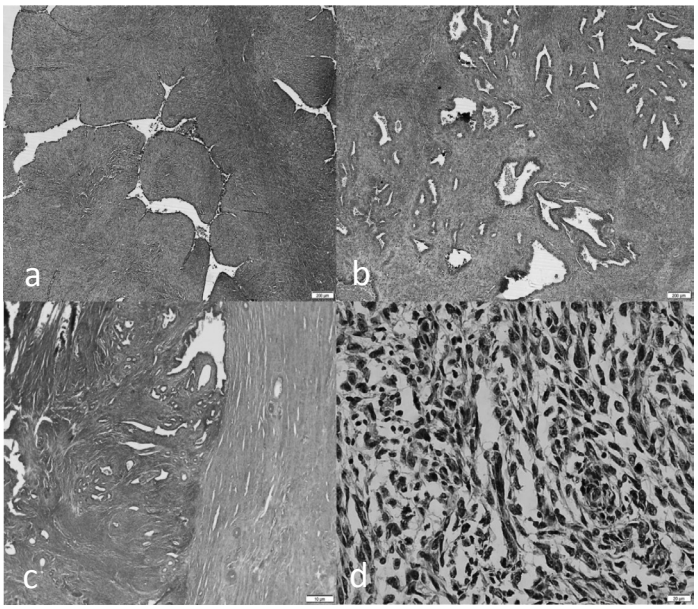

Figure 5. a. Leaf-like architectural pattern lined by bland appearing epithelium resembling phyllodes tumor of the breast. **(H & E 40x). b.** Presence benign glandular element with periglandular cuffing of stromal component **(H & E400x). c.** Myometrium-tumor interface, characterized by an intimate admixture of benign endometrial glands (red arrow shows the myometrium) and sarcomatous stroma (yellow arrow) **(H & E 20x). d.** A sarcomatous overgrowth which demonstrates >25% high-grade stromal component with marked nuclear atypia and mitotic count. **(H & E 400x)**

hospital day, the ureteral stent was removed. The patient was discharged on the 12th hospital day.

Histopathology result showed mullerian adenosarcoma with sarcomatous overgrowth, thirteen centimeters in greatest tumor dimension, with more than fifty percent myometrial invasion and extension. Harvested lymph were negative for metastasis (Figure 5). The left adnexa was negative for tumor and the final stage for the index case is stage IC.

A panel of immunostaining such as estrogen receptors, progesterone receptors and CD 10 was done. The results showed ER was diffusely and strongly postive in the glandular component and focally and weakly postive in the stromal component (Figure 6a). The PR was diffusely postive in both the galndular and stromal components (Figure 6b) and there was loss of expression of CD 10 (Figure 6c).

DISCUSSION

Malignant stromal tumors account for 1-3% of all female genital tract tumors and Mullerian adenosarcomas (MAs) constitute 8-10% of these malignancies[2]. MASO is a unusual variant of uterine sarcomas which can be present in 10% of adenosarcomas[2]. It is usually seen in postmenopausal women, with median age of 58 years. However, cases of MASO are reported to occur relatively earlier, with median age 54.5 years old[1,2]. This is the second reported case in the Philippines since 1995 and the first to be reported in a reproductive age group [5].

Vaginal bleeding is the most common symptom occurring in seventy-one percent (71%) of patients with MASO[1,6]. They primarily present with uterine enlargement, prolapsed mass from the cervical OS, and or recurrent endometrial polyp[1,6]. The index case complained of a three-year history of abnormal vaginal bleeding accompanied with recurrent endometrial polyp. Due to the benign histologic results of the previous biopsies, strict follow-up was not emphasized and patient was complacent.

There are several risk factors that have been linked to

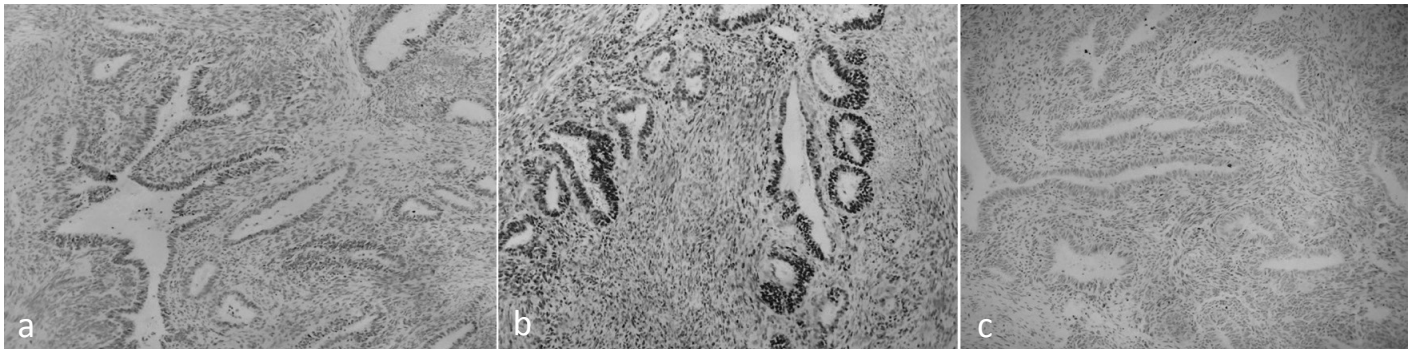

Figure 6. Immunohistochemical stains: a. ER: Diffusely positive in glandular component and focally and weakly positive in stromal component. **b.** PR: Diffusely and strongly positive in both glandular and stromal components. **c.** CD 10: Negative in cells of interest.

the increased risk of adenosarcoma, such as hyperestrogenism, long term oral contraceptive use, tamoxifen, chemotherapy and radiotherapy[2,3,6] Hyperestrogenism is usually seen in among patients who are nulligravid, obese, diabetic, primary infertility and irregular menstruation[2,3,6]. The identifiable risk factors present were attributed to hyperestrogenism, primary infertility, history of abnormal uterine bleeding, endometrial hyperplasia and recurrent endometrial polyp[4,7,8]. Polyps may appear in areas where there is an increased expression of estrogen receptors and its presence have reported to increase the risk for endometrial carcinoma to nine times more than patients without polyps[7]. However, there is no clear association between recurrent polyps and sarcomatous transformation, specifically in the reproductive age group[7,8]. The molecular tumorigenesis is still unclear and has no proven etiologic factors but it has several links with hyperestroginsm[3,7,9,10].

It has distinguishing histologic characteristics that involves a complex integration of morphological and immunohistochemical results. It appears as a polypoid mass with biphasic components of benign epithelial elements and a sarcomatous stroma[1,4]. There is a Leaf-like architectural pattern lined by bland appearing epithelium resembling phyllodes tumor of the breast (Figure 5a). There is presence of benign glandular element with periglandular cuffing of stromal component (Figure 5b). Myometrium-tumor interface, characterized by an intimate admixture of benign endometrial glands and sarcomatous stroma (Figure 5c). The index case has a sarcomatous overgrowth demonstrates >25% high-grade stromal component which is typically high grade, with increased cellularity and mitotic activity and greater nuclear atypia as compared to the appearance of the background adenosarcoma. Aside from the H and E, a panel of immunohistochemical staining can confirm the diagnosis of MASO. Pathologic analyses of uterine adenosarcoma have identified estrogen receptor (ER) positivity in approximately 80% and progesterone receptor (PR) positivity in 65% to 80% of cases. The incidence of hormone receptor positivity is lower or weaker in patients with sarcomatous overgrowth[11]. This is in contrast to the index patient where there is highly positive hormone receptors. The results of ER was diffusely and strongly positive in the glandular component but focally and weakly positive in the stromal component (Figure 6a). The PR was diffusely positive in both the glandular and stromal components (Figure 6b). An additional immunostaining such as CD 10 was performed to aid in differentiating and confirming the histologic diagnosis. The mesenchymal cells in adenosarcoma typically shows cytoplasmic staining for CD10, but it is often weaker or lost in areas of high-grade sarcomatous overgrowth (Figure 6c)[2,9,12]. The index case showed loss of CD 10 which supports our diagnosis. It is important to distinguish adenosarcoma from MASO, since the latter is considered to be poor prognostic indicator.

Most of the cases of MASO were managed by primary surgery with complete staging to remove all sites of disease[1,5,11,12]. It can be curative if disease is confined to the uterus with a 50% 5-year survival[1]. The NCCN practice guidelines version 2016 for uterine sarcoma recommends primary surgery but benefit of lymphadenectomy is still controversial[13]. However, the guideline was limited for leiomyosarcoma, low grade endometrial stromal (ESS) and high grade stromal tumors[13]. In the SGOP guidelines, adenosarcoma and ESS are managed the same treatment except for hormone therapy[14,15]. In the report of Carol and colleagues, wherein they reviewed 100 cases of uterine adenosarcoma, they have showed that among the reviewed cases. Out of seventy two patients (97%) who underwent hysterectomy, twenty-two patients (30%) had lymphadenectomy at the time of surgery and only one of these patients (4%) was diagnosed with a lymph node micro metastasis suggesting that lymphadenectomy may not be a necessary part of the at the primary surgical treatment[11]. This patient also had sarcomatous overgrowth and disease spread to the adnexa and cervix. Hence, lymphadenectomy showed no improvement in progression free survival, disease specific survival and overall survival compared to those without lymphadenectomy on univariate and multivariate analysis[11]. However, with sarcomatous overgrowth these are more likely to have nodal metastasis, hence complete staging should be done. In the study of Bagaria and colleagues, they have reported nodal metastases in 3.1% of 262 women who underwent a lymphadenectomy for adenosarcoma, but it was not specified whether or not women with nodal metastases had sarcomatous overgrowth[17].

Most cases are commonly reported in post-menopausal women hence ovarian conservation is not a dilemma. However, ovarian preservation in women of reproductive age may be an option in cases of early, non-metastatic disease. In a cohort of 60 patients with adenosarcoma 5 of 60 patients (8%) that underwent bilateral salpingooophorectomy had ovarian metastases without any other evidence of extrauterine disease, one had grossly abnormal adnexa, two grossly normal ovaries, and two other cases, did not specify the appearance of the ovaries[11]. The overall low reported rates of ovarian metastases in premenopausal women with uterine adenosarcoma, appears to be the absence of gross involvement. However, ovaries were castrated due to the risk of residual microscopic disease, recurrence and the role of estrogen is not fully known due to the rarity and limited literatures.

There is no consensus on the role of adjuvant treatments. In the study of Carrol and colleagues, support the use of adjuvant therapy with sarcoma-based chemotherapy regimens such as doxorubicin and ifosfamide for sarcomatous overgrowth[10-12]. However,

the role of radiotherapy for better local pelvic control is uncertain. The index case did not receive any adjuvant treatment since she was lost to follow-up.

The prognosis of MASO is poor due to its aggressive behavior associated with early post-operative recurrence, metastasis and fatal outcome. Clement reviewed ten patients who underwent surgery and reported that three patients were alive with no evidence of disease, seven had recurrence at intervals of nine months to six years, and six patients died from tumor progression at intervals of nine months to ten years[16]. The overall median survival time is thirteen months, but recurrence can occur as early as two weeks as reported by Farhat and colleagues[1].

Our patient presented with a rare tumor with rare tendency in a reproductive age group which makes the clinical suspicion very low, complacency, resulting in delay in diagnosis and treatment. It has a distinct histologic features which warrants a meticulous and correct multi-sections review of such rare tumors. It is very important for a precise histologic diagnosis since it has a clinical aggressive course which can affect its management and patient's psychological behavior towards treatment. A timely diagnosis and intervention is warranted due to the aggressive and lethal behavior which is associated with poor prognosis.

CONCLUSIONS

Our patient presented with a rare tumor with rare tendency in a reproductive age group which makes the clinical suspicion very low, resulting in delay in diagnosis and treatment. The rarity of MASO imposes a diagnostic challenge to the clinician. At present there are still no standard of care for the primary treatment and adjuvant therapy due to the paucity of studies. The occurrence of MASO to the reproductive age group possess more therapeutic problem with regards to ovarian preservation.

It is important for clinicians to have high index of suspicion for patients who presents with recurrent endometrial polyp because hyperestrogenism may be a risk factor for developing MASO.

Reporting of this cases is important for us to have a better understanding of the disease with regards to its tumorigenesis, course and treatment with the hopes of improving the survival advantage and prognosis. ■

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