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A rare case of extragenital Müllerian adenosarcoma

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Abstract:

A 51-year-old gravida 5 para 5 (5005) presented with an increasing abdominal girth and a palpable abdominal mass. She was initially diagnosed with ovarian new growth and underwent exploratory laparotomy. Intraoperatively, the uterus, Fallopian tubes, and ovaries were grossly normal and a large mass was seen attached to the cecum where the appendix should be referral to surgery service was done. Right hemicolectomy and ileostomy were performed. The histopathology report was "suggestive of a Müllerian adenosarcoma (MAS) involving the appendix and cecum." Microscopic examination showed evidence of endometriosis with no evidence of sarcomatous overgrowth, features that are favorable prognostic factors associated with higher disease-free survival. Postoperatively, the plan of management was hormonal therapy. Extragenital MAS is rare. This case is the fourth case to be reported in the literature to arise from the colon. Although there is still no standard of treatment, accurate diagnosis is imperative for appropriate management.

Keywords:

Appendix, cecum, colon, endometriosis, extragenital Müllerian adenosarcoma

Introduction

Müllerian adenosarcoma (MAS) of the female genital tract is a rare tumor of low malignant potential consisting of benign epithelial and malignant mesenchymal components.[1,2] It typically involves the uterus but it may also arise in extrauterine sites such as the ovaries, Fallopian tubes, cervix, and vagina and extremely rare in extragenital sites such as the peritoneum, retroperitoneum, bladder, liver, and colon.[1,3]

It is the rarest form and is only 5%–9% of all uterine sarcomas representing approximately 0.2% of all uterine malignancies. As of 2018, only 32 cases of extragenital MAS have been reported in the literature.[1] Only three developed from the colon.[4,5]

Adenosarcoma has the highest incidence in perimenopausal or postmenopausal women.[2] In a review of cases by Mandato *et al.*, extrauterine and extraovarian MAS occurs in younger women than in uterine MAS. At diagnosis, the mean age was 45 years old compared to 58 years old in uterine MAS. In the same review, other clinical features of extrauterine and extraovarian MAS have been described. Unlike uterine MAS, wherein bleeding is the most common presenting symptom, extrauterine and extraovarian MAS present as a large abdominal mass associated with abdominal pain, urinary disorders, anorexia, abdominal pain pressure, and fatigue. The tumor size reported ranged from 2.5 to 34 cm. CA-125 was elevated in 63% of the cases, which may be related to the association with endometriosis. A history of endometriosis was present in 61% of the cases. And finally, 20% of cases received hormonal therapy such as estrogen replacement therapy or tamoxifen.

Case Report

The index patient is a 51-year-old gravida 5 para 5 (5005) who presented with an 11-month history of increasing abdominal girth and a palpable abdominal mass. She has been menopause for 1 year and has

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no history of hormonal replacement therapy use. She reported having dysmenorrhea.

The patient sought to consult with a general practitioner. Whole abdominal ultrasound showed a large complex, predominantly cystic, multiseptated abdominopelvic mass measuring 19 cm × 17.6 cm × 21.6 cm, and probably ovarian in origin. Two months later, a whole abdominal computed tomography scan with contrast showed that the mass now measures 25.29 cm × 31.56 cm × 30.58 cm, well-circumscribed, complex, predominantly cystic with enhancing solid components. One month before admission, she consulted at our institution for further evaluation and management. She did not present with vaginal bleeding. On gynecologic evaluation, there was a palpable cystic mass up to the level of the xiphoid process and nontender [Figure 1]. Transabdominal and transvaginal ultrasonography with Doppler studies showed a multilocular solid cyst measuring 40.98 cm × 40.09 cm × 33.24 cm with the scanty scattered intratumoral flow and a thickened endometrium measuring 0.78 cm with absent color flow [Figure 2]. CA-125 and HE4 were 45.48 units/ml and 83.89 pmol/L, respectively, both elevated.

The primary consideration was an ovarian new growth, probably malignant; hence, the plan of management was to do a total abdominal hysterectomy with bilateral salpingo-oophorectomy with surgical staging and evaluation of the endometrium. On exploratory laparotomy, a large mass was seen where the appendix should be located [Figure 3]. The ovaries and fallopian tubes appeared grossly normal, whereas the uterus had bleb-like lesions at the posterior upper corpus but was otherwise normal-looking [Figure 4] and therefore was left behind. Endometrial curettage was done to rule out endometrial pathology. At this point, the diagnosis was changed to appendiceal mucocele versus appendiceal malignancy; hence, the right hemicolectomy and ileostomy were performed. Gross findings showed an appendiceal mass measuring 28 cm in greatest diameter with one dominant cyst locule and thick solid wall measuring up to 5 cm. There was no recognizable appendix. The ileum and the rest of the colon were grossly unremarkable. Microscopic findings suggest MAS involving the serosa and subserosa of the appendix and cecum, whereas the endometrial curettings showed atrophic endometrium. Postoperatively, the plan of management was treatment with megestrol acetate 160 mg once a day. Immunohistochemical studies yielded positive results for estrogen receptor (ER) and progesterone receptor (PR).

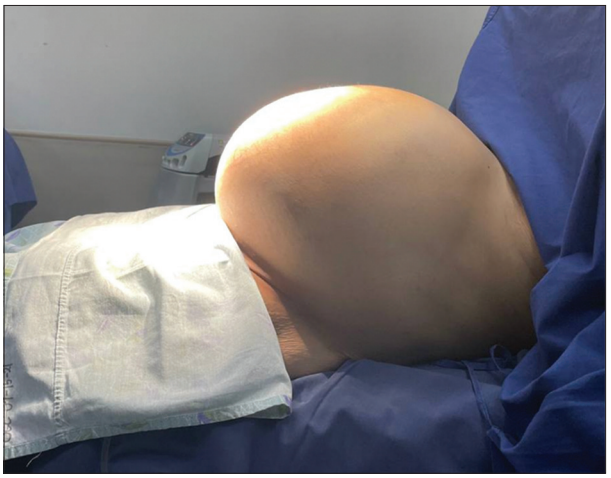

Figure 1: There is a palpable cystic mass up to the level of the xiphoid process

Case Discussion

The index case was diagnosed with ovarian new growth that turned out to be an appendiceal mass, for which the histologic diagnosis was an extragenital MAS involving the appendix and cecum.

MAS is characterized as a biphasic tumor exemplified by the presence of an epithelial elements that are benign and mesenchymal components that are low-grade malignant.[6] The epithelial elements are usually in the form of glands, which are widely separated by the abundant stromal component. Most often low grade, the stromal component comprises spindle-shaped and round cells [Figure 5]. One of the most characteristic features of adenosarcoma is periglandular cuffing showing condensation of stromal cells around the glandular elements [Figure 6].[7]

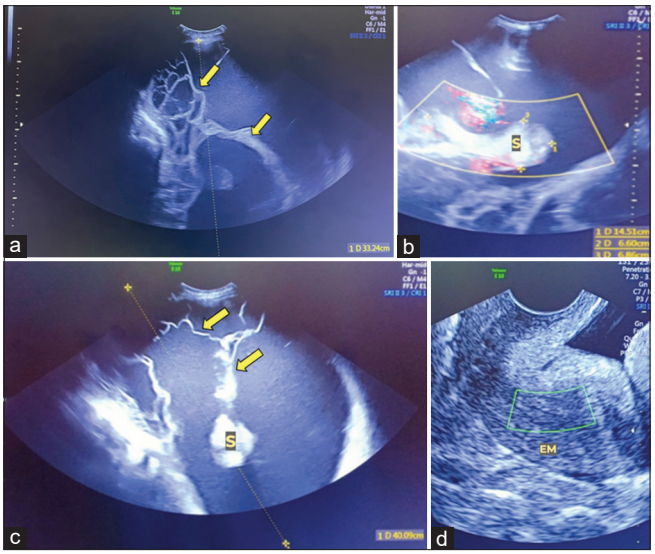

Figure 2: Images of patient's transvaginal ultrasonography with Doppler studies. (a and c) Occupying the abdominopelvic cavity is a mass with multiple locules and solid areas (S) with multiple septations (arrows). (b) Doppler studies show scanty intratumoral flow around the solid areas (S). (d) The EM was 0.78 cm thick and Doppler studies show absent color flow. Impression: Normal-sized anteverted uterus. Normal cervix. Thickened endometrium. Abdominopelvic mass consider ovarian new growth probably malignant. EM: Endometrium

There are limited reports on extragenital MAS. This is only the fourth case reported in the literature that developed in the colon.[4,5] How did it arise in this location? There are three main theories on its pathogenesis. First, extrauterine tumors are thought to arise from endometriotic deposits. It can be associated with or may have developed from underlying endometriosis, the most likely origin in the index patient.[1,4] Second, especially in cases where endometriosis is not present, adenosarcoma may have developed from pluripotent mesenchymal cells within the pelvic cavity. Finally, this kind of adenosarcoma can also occur from Müllerian-duct remnants incorporated within other normal organs during organogenesis.[1,6] Most cases are associated with endometriosis.[6] The index patient has no known history of endometriosis but reported having dysmenorrhea. Intraoperatively, bleb-like lesions were noted at the posterior upper corpus. Thus, pelvic endometriosis was considered. Histologically, endometriotic sites [Figure 7] were seen at the junction between the mass and the cecum. This case satisfies Sampson's criteria for malignant transformation of endometriosis which include the following endometriotic sites were found closely associated with the malignancy, the histological characteristics are compatible with an endometrial origin, and no other primary tumor was observed.[8] The histological link between endometriosis and cancer was first postulated by Sampson a few years after his theory of retrograde menstruation. Endometrial tissue, wherever situated, usually reacts to menstruation, pregnancy, and menopause, as does the mucosal lining in the uterine cavity. Thus, they are governed by the same natural laws as the latter, and one would deduce that they would be subjected to similar pathologic changes. That is, they have the same potentiality for malignant changes as in the endometrium.[7] Malignant transformation is a rare occurrence with an incidence of <1%.[4] Malignant change in endometriosis is more

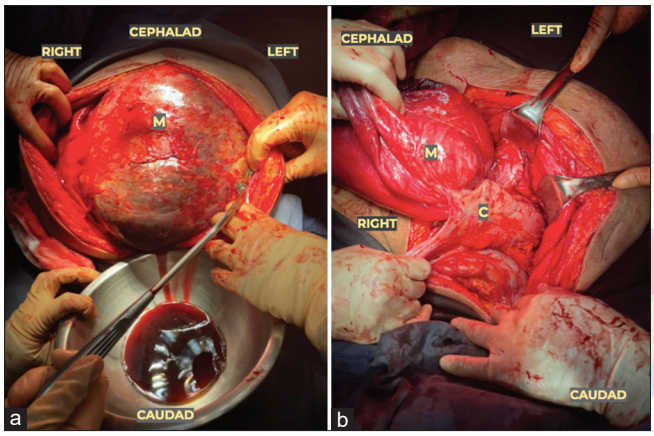

Figure 3: (a) A large mass (M) was seen occupying the abdominal cavity. (b) The mass (M) was attached to the cecum (C) in the area where the appendix is supposed to be located. No identifiable appendix was seen

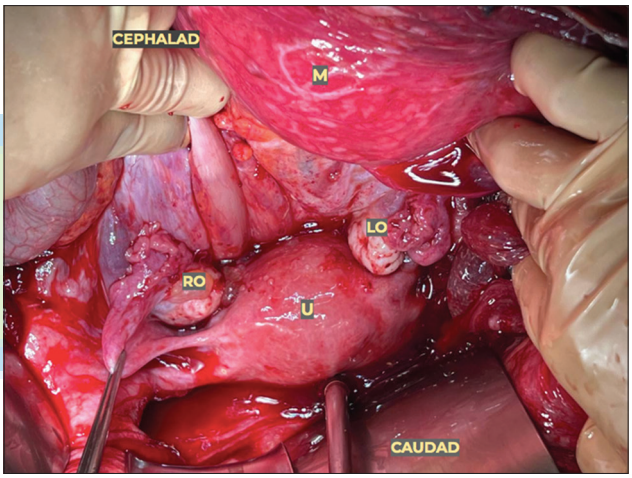

Figure 4: The uterus, Fallopian tubes, left ovary, and right ovary appeared grossly normal. M: Mass, U: uterus, LO: Left ovary, RO: Right ovary

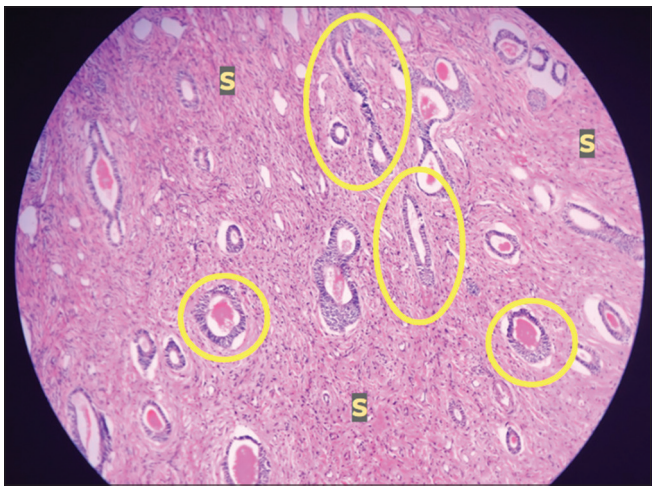

Figure 5: Low-power microscopic view of the specimen showing epithelial elements in the form of dilated and slit-like glands (encircled) widely separated by an abundant low-grade stromal (S) component which is characteristic of adenosarcoma

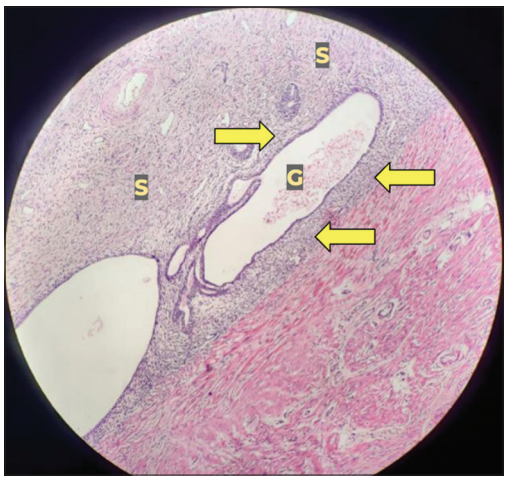

Figure 6: Low-power microscopic view of specimen showing the stromal cells concentrate around the glandular (G) elements called periglandular cuffing (arrows), a characteristic feature of adenosarcoma. S: Stroma

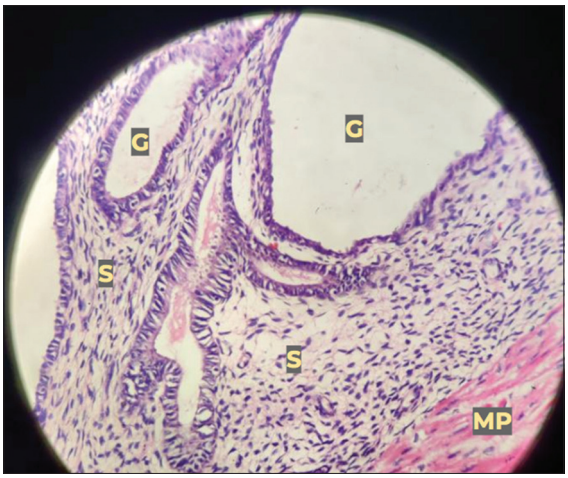

Figure 7: High-power microscopic view showing an endometriotic focus involving the serosa and subserosa of the cecum. G: Gland, S: Stroma, MP: Muscularis propria

widely seen in ovarian endometriosis.[8] A review of pathologic slides from 1000 cases of surgically proven endometriosis found a 0.3% rate of adenosarcoma in cases of extraovarian endometriosis.[9] The association of endometriosis with extrauterine tumorigenesis is considered a favorable prognostic factor.[1] Risk factors for transformation such as pelvic irradiation and chronic stimulation with endogenous or exogenous estrogen may increase the likelihood of endometriosis-associated carcinogenesis.[6] The index patient has not been subjected to pelvic irradiation and she has never had previous hormone therapy.

For the histologic diagnosis of adenosarcoma, the World Health Organization requires the presence of significant stromal cellularity with periglandular cuffing, a stromal mitotic count of 2 or more/10 high-power fields, and atypia of stromal cells.[2] This case presented observable periglandular cuffing, stromal mitotic count of more than 2/10 high-power fields, and mild-to-moderate stromal cell atypia. There are no immunohistochemical markers that are pathognomonic for adenosarcoma. The diagnosis is dependent mainly on morphologic features.[10] The most common immunohistochemical markers used are CD10 and Wilms' Tumor 1, similar to endometrial stromal tumors. The epithelial component stains for cytokeratins, epithelial membrane antigen, PR, and ER. There is a loss of CD10, ER, and PR expression in cases of sarcomatous overgrowth, in which the sarcomatous component occupies more than 25% of the tumor.[6,10] Sarcomatous overgrowth is an unfavorable prognostic factor.[1] Immunohistochemistry studies have limited application to the diagnosis of adenosarcoma but may be necessary for differentiating those with sarcomatous overgrowth and may provide biological insights into the possible efficacy of hormonal therapy.[11]

In a mass presenting in the gastrointestinal tract with a histopathologic finding suggestive of Müllerian origin, the initial dilemma was determining if the mass is truly primary endometrial or primary colonic in origin. This is important to discuss because accurate diagnosis is crucial for appropriate management.

According to Yantis *et al.*, the histologic location of the lesion can provide supportive evidence regarding the true origin of the mass. Primary colonic carcinomas always involve the mucosa and extend toward the serosal surface. In contrast, endometriosis and cancers arising in it commonly involve the outermost layers of the bowel wall, including the serosa, subserosa, and muscularis propria.[4] In this case, the tumor involved the serosa and subserosa of the appendix and cecum thus it is likely to have developed from an endometriotic implant on the colon.

Due to its rarity, there are no available guidelines for treatment specifically for extragenital MAS. For uterine MAS, on the other hand, the primary treatment is hysterectomy with bilateral salpingo-oophorectomy.[12] In the review of cases by Mandato *et al.*, complete surgical resection represents the best course of action for extrauterine and extraovarian MAS. Patients who had a complete resection showed a higher overall survival rate than those who had partial resection. The overall survival of patients who underwent surgical resection was more favorable than those who underwent surgery with adjuvant treatment or those who did not undergo surgery at all.[1] Should the total abdominal hysterectomy with bilateral salpingo-oophorectomy been done in this case? In a case series by Clement *et al.*, they entertained the possibility that the extragenital adenosarcomas were recurrences of uterine tumors that were unrecognized in the hysterectomy specimens. However, this was highly unlikely because all the uterine sarcomas they reported recurred within 4 years after hysterectomy, and the site of recurrence was generally in the vaginal apex. In contrast, the hysterectomies in another series of cases they reported had been done 13–38 years before the discovery of the extragenital tumors.[13,14] Two of the three cases of an extragenital mass arising from the colon reported in the literature also underwent surgical tumor and colon resection only. Hysterectomies were not performed and no adjuvant therapy was given. They remained free of disease for 24 and 36 months.[4] Had the true diagnosis been known, it would have been prudent to proceed with total abdominal hysterectomy with bilateral salpingo-oophorectomy to determine if there was an associated uterine pathology. Since this pathology is rare, it is unlikely that the diagnosis be known before surgery in most cases and would only be made on the final histopathology.[12] MAS is relatively insensitive to chemotherapy and radiation.[15] The

optimal therapy for advanced or recurrent tumors has yet to be determined.

It is even more difficult to make recommendations on managing extrauterine adenosarcomas as they are so rare. However, management should be based on surgical principles. Local guidelines from the Society of Gynecologic Oncologists of the Philippines follow the same principles. Surgery is the primary treatment, hormonal therapy is an adjuvant treatment, especially for stages II to IV, and external beam radiation therapy or radiotherapy for persistent or recurrent disease.[16] In this case, the staging was not done due to problems with stage assignment since staging is based on myometrial invasion and the extent of disease outside the uterus. Hence is not applicable in extragenital adenosarcomas.

Hormone therapy is the recommended adjuvant treatment and is applicable in this case. Adenosarcomas' ER/PR positivity could be used as predictive biomarkers for response to hormonal therapy. Progesterone hormone therapy is beneficial in treating adenosarcoma and other endometrial malignancies due to the expected progesterone-induced suppression. Because most high-grade diseases lack ER and PR expression, hormone therapy should only be considered in low-grade ER-/PR-positive adenosarcomas without sarcomatous overgrowth.[3] Fortunately, the index patient is ER/PR positive and her histologic findings were negative for sarcomatous overgrowth.

In a case report by Hines *et al.* on extrauterine MAS treated with a combination of surgical resection and medroxyprogesterone acetate, they treated a 43-year-old woman with a background of endometriosis who presented with bilateral adnexal masses. Like in the index patient, the presumptive diagnosis was ovarian carcinoma, but the final histologic diagnosis was MAS. The primary treatment was surgical resection. She underwent subtotal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and tumor debulking. Some tumors remained adherent to the colon, resulting in suboptimal cytoreduction. Due to a lack of established chemotherapeutic protocol for treating disseminated adenosarcoma, a trial with megestrol acetate 40 mg four times/day for 5 weeks was initiated. Ten months postoperatively, this patient remained without evidence of disease.[15] The index patient is currently undergoing hormonal therapy with megestrol acetate.

Based on the data collected in the case series by Mandato *et al.*, several prognostic criteria were observed. The recurrence rate for uterine MAS was 23%, whereas 42% for extrauterine MAS. The likelihood of hematogenous metastasis was 2% for uterine MAS, whereas 33% for extrauterine MAS. Finally, the percentage who died secondary to MAS was 10% for the uterine form, whereas 28% for the extrauterine form.[1] According to Murugasu *et al.*, extragenital MAS is more aggressive than uterine MAS, and the aggressiveness may be due to the lack of the uterine myometrial wall as a barrier.[17] Hence, it is typically large at presentation and can easily spread to the peritoneum and the abdominopelvic organs. The association with endometriosis was a favorable prognostic factor and showed increased disease-free survival than adenosarcoma in patients without endometriosis.[1] Sarcomatous overgrowth, on the other hand, is associated with a worse prognosis. It is highly aggressive and is characterized by recurrence and metastasis at an early stage. Patients with uterine MAS showed a median overall survival of 161 months. The index patient presents with a relatively good prognosis for an extragenital MAS case due to the association with endometriosis and the absence of sarcomatous overgrowth.

Conclusion

In conclusion, the rarity of this case imposes a diagnostic challenge on the clinician. Diagnosis is dependent mainly on histopathologic characteristics. Immunohistochemistry has limited application in diagnosing adenosarcoma but may provide information on the efficacy of hormonal therapy and the presence of sarcomatous overgrowth. No guidelines have been created on the management of extragenital MAS due to limited data and the variability of its presenting features, but complete surgical resection represents the best course of action. Hormonal therapy should be considered in ER-/PR-positive MAS without sarcomatous overgrowth. The presence of endometriosis is a favorable prognostic factor, whereas the presence of sarcomatous overgrowth has been associated with higher rates of recurrence and decreased overall survival. The rarity of this case points us to consider this condition in a woman presenting with a pelvic mass with a history of endometriosis. As clinicians, more so as gynecologists, our clinical judgment plays a vital role in case management. Furthermore, given the limited guidelines on its management, it is crucial to establish appropriate referral systems. As an end, the case presented above is indeed a rare presentation of an extragenital MAS. This case has well contributed to the body of knowledge that could 1 day help establish a treatment standard.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names

and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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