The Relationship between Primary Extrauterine Adenosarcoma and the Secondary Müllerian System: Report of a Unique Case Demonstrating Histologic Transition between Benign and Malignant Elements and a Review of the Literature

Wei Liu, MD, PhD, Constantine A. Axiotis, MD

Abstract

Background: **Extrauterine adenosarcomata are thought to arise from pre-existing foci of endometriosis. In 1925 Sampson proposed three criteria for a definitive diagnosis of malignancy arising in endometriosis: (1) histological evidence of endometriosis in close proximity to the tumour; (2) no other identifiable primary site of malignancy; and (3) histological appearance of the tumour compatible with an origin in endometriosis. In 1953 Scott added a fourth criterion (4) requiring contiguous histological transition of benign endometriosis merging with the malignant component.**

Case Report: **We report an unusual and unique case of extrauterine müllerian adenosarcoma which fulfills both Sampson's and Scott's criteria and review the literature on extrauterine adenosarcoma and their relationship with the extended müllerian system. We also demonstrate that lymph node "metastases" of adenosarcoma may arise from pre-existing endometriosis.**

Conclusions: Our case is among the first to histologically demonstrate the histologic transition between endometriosis and extrauterine müllerian adenosarcoma.
[N A J Med Sci. 2010;3(3):132-135.]

Key Words: *Endometriosis; adenomyosis; extrauterine müllerian adenosarcoma; secondary müllerian system*

Received 05/10/2010; Revised 06/12/2010; Accepted 06/15/2010

Wei Liu, MD, PhD, Constantine A. Axiotis, MD
Department of Pathology, State University of New York, Downstate Medical Center and Kings County Hospital Center, Brooklyn, New York 11023, USA

(*Corresponding author)
Wei Liu, MD, PhD
Department of Hematopathology
1515 Holcombe Blvd, Unit 72
Houston, TX 77030
E-mail: wliu30@gmail.com

Introduction

Müllerian adenosarcomata are biphasic neoplasms composed of both benign müllerian glands and malignant sarcomatous elements. They occur most often within the endometrium[1] and less frequently the ovary.[2-5] Rare and unusual sites include the peritoneum,[6-10] intestine,[11,12] vagina,[13-15] urinary bladder,[16,17] liver,[18,19] and round ligament.[20] Intrauterine adenosarcomata are considered stromal neoplasms which induce gland formation and proliferation.[21,22] Extrauterine tumors are thought to arise from pre-existing foci of endometriosis if they fulfill the following criteria: a) histological evidence of endometriosis in close proximity to the tumor; b) no other identifiable primary site of malignancy; and c) histological appearance of the tumor compatible with an origin in endometriosis.[23] A more stringent criterion, d) contiguous histological transition of endometriosis merging with the malignant component[24] has not been universally applied. We report an extrauterine müllerian adenosarcoma with histological transition to areas of endometriosis and review the literature.

Case Report

A 37-year-old nulliparous woman presented with increasing abdominal girth and discomfort for one month. Pelvic examination suggested an enlarged uterus and adenexa confirmed by Computerized tomography (CT) of the abdomen and pelvis. In addition CT demonstrated extensive abdominal ascites, retroperitoneal lymphadenopathy, subcapsular hypodense hepatic lesions, and an ill-defined enhancing greater omentum and peritoneum. Exploratory laparotomy revealed a diffuse 25 cm pelvic mass, involving the uterus and both ovaries, the serosa of the sigmoid colon, the paraaortic lymph nodes, omentum, and the liver. Tumor debulking was performed together with a supracervical hysterectomy and bilateral salpingo-oophorectomy, sigmoid resection, omentectomy and left para-aortic lymphadenectomy.

Gross pathologic examination revealed an extensive, nodular and diffuse neoplasm infiltrating the uterine serosa, and ovaries as well as the sigmoid colon, mesocolon, hepatic capsule, and para-aortic lymph nodes. Solid masses

measuring 7 cm x 6 cm x 5 cm and 6 cm x5 cm x 4 cm respectively obscured both ovaries. Two tumor masses were present on the serosal surface of sigmoid colon measuring 7 cm x2.5 cm x 2.4 cm and 6 cm x 1.6 cm x 1.3 cm. The omentum contained two polypoid tumor masses measuring 2 cm x 1.8 cm x 1.6 cm and 2.5 cm x1.9 cm x1.8 cm. Two subcapsular hepatic tumor nodules measuring 1.9 cm x1.7 cm x1.2 cm and 1.5 cm x1.0 cm x 0.9 cm were also present.

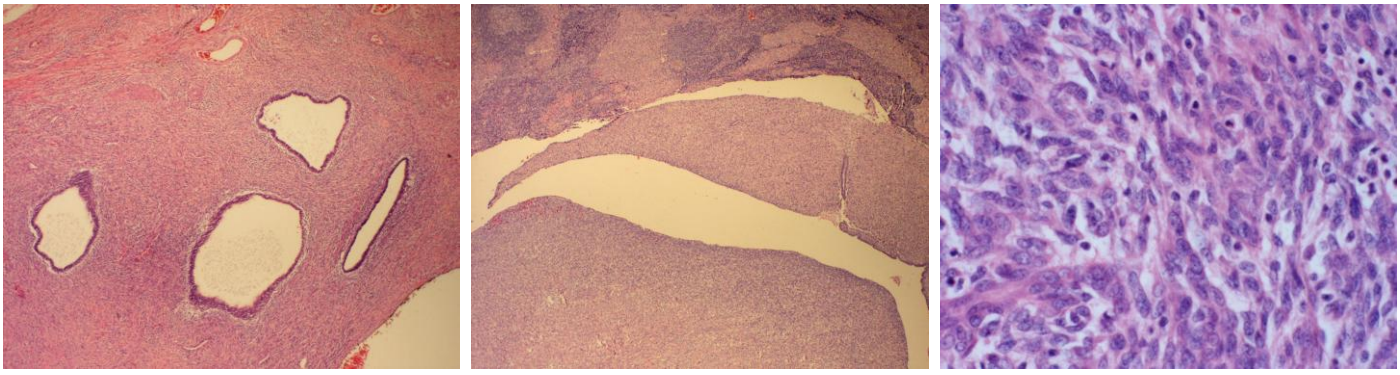

Figure 1a. Periglandular condensation of stroma. (left)
Figure 1b. Leaf like projection of stroma into the glandular space. (middle)
Figure 1c. Area with sarcomatous overgrowth. (right)

Microscopically, the tumor exhibited characteristic features of homologous müllerian adenosarcoma with sarcomatous overgrowth. The glandular component was predominantly endometrioid and to a lesser extent tubal-type with occasional foci exhibiting architectural atypia. Distinctive hypercellular and mitotically active periglandular stromal cuffs (**Figure 1a**) and polypoid stromal intraglandular invaginations were ubiquitous (**Figure 1b**). Noteworthy was the extensive sarcomatous overgrowth accounting for approximately 95% of the total tumor volume (**Figure 1c**). These areas were composed of either round or spindle cells with marked atypia and resembled endometrial stromal sarcoma, leiomyosarcoma, or fibrosarcoma. Foci of lymphoplasmacytic cells were identified within the sarcomatous areas.

There was concurrent adenomyosis and ovarian, colonic and lymph nodal endometriosis intimately associated with the adenosarcoma. The adenomyosis extensively involved the outer half of myometrium and demonstrated transition to asdenosarcoma (**Figure 2a**). Similarly foci of ovarian, colonic, and lymph nodal endometriosis demonstrated histologic transition to adenosarcoma (**Figure 2b**).

Discussion

In 1978 Clement and Scully, in a series of cases demonstrating concomitant endometriosis and adjacent adenosarcoma, first proposed that extrauterine müllerian adenosarcomata arise from endometriotic deposits and/or pluripotent mesothelial and mesenchymal cells of the secondary mullerian system.[4] We reviewed the literature between 1977 and 2008 for all reported cases of extrauterine müllerian adenosarcoma in association with endometriosis and found 24 pathologically documented cases (**Table 1**).[3-5,7-9,10-12,13,15-19,25-27] Twenty-one of 24 cases met Sampson's

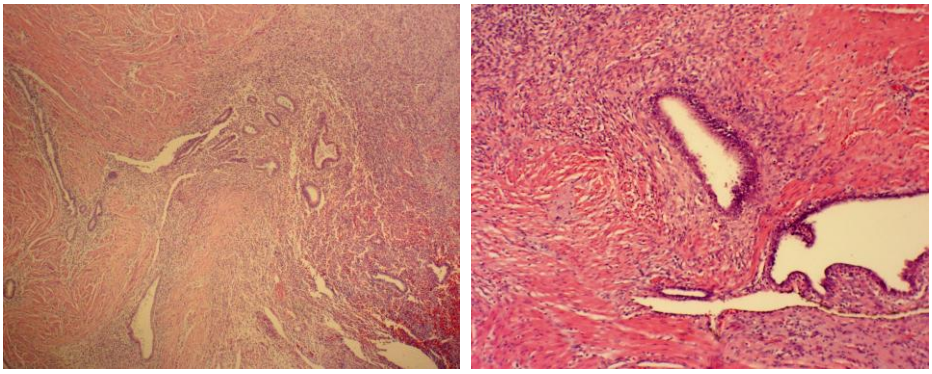

Figure 2a. Transition of endometriosis (arrow) to adenosarcoma (arrowhead). Uterine wall. (left)
Figure 2b. Transition of endometriosis (arrowhead) to adenosarcoma (arrow). Intestinal wall. (right)

Table 1. Extrauterine adenosarcoma arising in association with endometriosis between 1977-2008.

Case #	Authors (ref)	Year	Site	Does the case meet Sampson's criteria of malignancy arising from endometriosis? (yes or no)	Is there a transition zone from endometriosis to adenosarcoma? (yes or no)
1	Mahoney et al.(10)	1977	pelvic	no	no
2	Clement et al. (4)	1977	left pelvic wall	no	no
3	Clement et al.(4)	1977	left ovary	no	no
4	Vara et al.(17)	1990	bladder	yes	no
5	Mckay et al.(9)	1993	perirectal	yes	no
6	Judson et al.(15)	2000	vagina	yes	no
7	Yantiss et al.(12)	2000	small bowel	yes	no
8	Yantiss et al.(12)	2000	small bowel	yes	no
9	Yantiss et al.(12)	2000	colon	yes	no
10	Yantiss et al.(12)	2000	sigmoid	yes	no
11	Slavin et al. (11)	1999	terminal ileum	yes	no
12	N'Senda et al.(19)	2000	liver	yes	no
13	Andersen et al.(14)	2001	vagina	yes	no
14	Dincer et al.(8)	2001	peritoneal	yes	no
15	Hines et al.(5)	2002	ovary	yes	no
16	Nezhat et al.(16)	2002	bladder	yes	no
17	Liu et al.(13)	2003	vagina	yes	no
18	Raffaelli et al.(7)	2004	pelvic	yes	no
19	Jelovsek et al.(18)	2004	liver	yes	no
20	kondi-pafiti et al.(3)	2004	ovary	yes	no
21	Chang et al.(6)	2005	pelvic	yes	no
22	Milam et al. (25)	2006	Inguinal	yes	no
23	Shetty et al. (26)	2007	ovary	yes	no
24	Manipadam et al.(27)	2008	ovary	yes	no
25	Current case	2005	adnexa	yes	yes

criteria[23] for malignancies arising from endometriosis; however, no case histologically demonstrated a transition between endometriosis and adenosarcoma as first proposed by Scott[24] confirming an endometriotic origin. In our case, endometriosis was present in ovaries, muscularis propria and subserosa of the colon, and para-aortic lymph node; the endometriotic foci were adjacent to sarcomatous tissue in each site and most importantly there was histological transition from endometriosis to adenosarcoma in both the muscularis propria of colon and para-aortic lymph node. Furthermore, there was also histologic transition between adenomyosis in the outer myometrium and the adenosarcoma in the outer uterine surface, suggesting a concurrent uterine adenosarcoma arising from adenomyosis.

Mullerian adenosarcomata most often arise from uterine endometrium. Less frequently they originate from the serosal surface of the uterus in association with adenomyosis.[28] Adenosarcomata of the adnexae are both rare and indicative of worse prognosis than their uterine counterparts. The current case describes an adenosarcoma simultaneously present on the uterine serosal surface and bilateral adnexae. When tumors are synchronously found in uterus and ovary at the time of initial diagnosis, it is of difficult interpretation to determine a uterine or adnexal origin. Primary ovarian tumors are often unilateral; and by convention, concurrent uterine and bilateral ovarian involvement is considered presumptive evidence of uterine primary, as in the case of epithelial neoplasms.[28]

In this case distinct and separate tumor nodules were also present in the sigmoid colon, omentum, hepatic surface, and a para-aortic lymph node. The tumorigenesis of extrauterine mullerian adenosarcoma is more complex. Two mechanisms are considered: 1) origin from preexisting endometriosis, and 2) origin from the secondary müllerian system of Lauchlan.[29] The demonstration of a transition zone from endometriosis to the tumor in our case is strongly supportive of this

mechanism. In the broader sense, however, the origin of both extrauterine mullerian adenosarcoma and endometriosis may be viewed as derivative of the secondary müllerian system. The secondary müllerian system is composed of cells that mimic the lining epithelia of cervix, uterus, and oviducts. These cells have no distinct organization and their differentiation and proliferation subsequent to a variety of stimuli is thought to contribute to the genesis of a wide range of lesions spanning from endometriosis and endosalpingiosis to serous and mucinous neoplasms of ovary as well as carcinosarcoma and adenosarcoma.[30]

Müllerian adenosarcoma usually spreads by contiguity to the pelvis and neighboring organs. However, distal metastasis to lung, brain, and other organs has been reported. The metastases are usually pure sarcoma.[1] Lymphangitic dissemination of adenosarcoma is extremely rare. In a review done by Kaku et al. only two of thirty one cases of adenosarcoma of uterus were reported to have pelvic lymph node metastases.[31] In our case the lymph node involvement was of difficult interpretation. Foci of endometriosis were present subcapsularly with transitional areas to adenosarcoma indicative of synchronous tumor generation rather than lymphatic metastases; however, within the same lymph node there was also the presence of sarcomatous stroma directly in the subcapsular sinus consistent of metastasis.

In conclusion, we report a case of uterine and extrauterine müllerian adenosarcoma associated with and displaying histological transition with both adenomyosis and endometriosis. Additionally, we show histologic transition from endometriosis to adenosarcoma within a para-aortic lymph node supporting the idea that presumed intranodal metastases may in actuality represent concurrent tumorigenesis. Liberal histologic sampling is paramouint in uncovering these transitional areas.

References

1. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathological analysisof 100 cases with a review of the literature. Human Pathology. 1990;21(4):363-381.
2. Eichhorn JH, Yang RH, Clement PB, Scully RE. Mesodermal (mullerian) adenosarcoma of the ovary. Am J Surg Path. 2002;26(10):1243-1258.
3. Kondi-Pafiti A, Spanidou-Carvouni H, Papadias K, Hatzistamou-Kiari I, Kontogianni K, Liapis A, Smyrniotis V. Malignant neoplasms arising in endometriosis: clinicopathological study of 14 cases. Clin Exp Obstet Gynecol. 2004;31(4):302-304.
4. Clement PB, Scully RE. Extrauterine mesodermal (mullerian) adenosarcoma: a clinicopathologic analysis of five cases. Am J Clin Pathol. 1978;69(3):276-283.
5. Hines BJ, Porges RF, Mittal K, Muggia FM, Curtin JP. Use of medroxyprogesterone acetate in the treatment of Mullerian adenosarcoma: a case report. Gynecol Oncol. 2002;85(1):192-195.
6. Chang HY, Changchien CC, Chen HH, Lin H, Huang CC. Extrauterine mullerian adenosarcoma associated with endometriosis and rectal villotubular adenoma: report of a case and review of the literature. Int J Gynecol Cancer. 2005;15(2):361-365.
7. Raffaelli R, Piazzola E, Zanconato G, Fedele L. A rare case of extrauterine adenosarcoma arising in endometriosis of the rectovaginal septum. Fertil Steril. 2004;81(4):1142-1144.
8. Dincer AD, Timmins P, Pietrocola D, Fisher H, Ambros RA. Primary peritoneal mullerian adenosarcoma with sarcomatous overgrowth associated with endometriosis: a case report. Int J Gynecol Pathol. 2002;21(1):65-68.
9. Mckay DC, Ellis JH, Marn CS. CT of mullerian adenosarcoma arising in endometriosis. Clin Imaging. 1993;17(3):204-206.
10. Mahoney AD, Waisman J, Zeldis LJ. Adenomyoma: a precursor of extrauterine Mullerian adenosarcoma? Arch Pathol Lab Med. 1977;101(11):579-584.
11. Slavin RE, Krum R, Van Dinh T. Endometriosis-associated intestinal tumors: a clinical and pathological study of 6 cases with a review of the literature. Hum Pathol. 2000;31(4):456-463.
12. Yantiss RK, Clement PB, Young RH. Neoplastic and pre-neoplastic changes in gastrointestinal endometriosis: a study of 17 cases. Am J Surg Pathol. 2000;24(4):513-524.
13. Liu L, Davidson S, Singh M. Mullerian adenosarcoma of vagina arising in persistent endometriosis: report of a case and review of the literature. Gynecol Oncol. 2003;90(2):486-490.
14. Anderson J, Behbakht K, De Geest K, Bitterman P. Adenosarcoma in a patient with vaginal endometriosis. Obstet Gynecol. 2001;98:964-966.
15. Judson PL, Temple AM, Fowler WC Jr, Novotny DB, Funkhouser WK Jr. Vaginal adenosarcoma arising from endometriosis. Gynecol Oncol. 2000;76(1):123-125.
16. Nezhat CH, Malik S, Osias J, Nezhat F, Nezhat C. Laparoscopic management of 15 patients with infiltrating endometriosis of the bladder and a case of primary intravesical endometrioid adenosarcoma. Fertil Steril. 2002;78(4):872-875.
17. Vara AR, Ruzics EP, Moussabeck O, Martin DC. Endometrioid adenosarcoma of the bladder arising from endometriosis. J Urol. 1990;143(4):813-815.
18. Jelovsek JE, Winans C, Brainard J, Falcone T. Endometriosis of the liver containing mullerian adenosarcoma: case report. Am J Obstet Gynecol. 2004;191(5):1725-1727.
19. N'Senda P, Wendum D, Balladur P, Dahan H, Tubiana JM, Arrive L. Adenosarcoma arising in hepatic endometriosis. Eur Radiol. 2000;10(8):1287-1289.
20. Gollard R, Kosty M, Bordin G, Wax A, Lacey C. Two unusual presentations of mullerian adenosarcoma: case reports, literature review, and treatment considerations. Gynecol Oncol. 1995;59:412-422.
21. Katzenstein AA, Askin FB, and Feldman PS. Mullerian Adenosarcoma of the uterus: an ultrastructural study of four cases. Cancer. 1977;40:2233-2242.
22. Roth LM, Pride GI, and Sharman, HM. Mullerian adenosarcoma of the uterine cervix with heterologous elements. A light and electron microscopic study. Cancer. 1976;36:1725-1736.
23. Sampson JA. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. Arch Surg. 1925;10:1-72.
24. Scott RB. Malignant changes in endometriosis. Obstetrics and Gynecology. 1953;2(3):283-289.
25. Milam MR, AtKinson JB, Currie JL. Adenosarcoma arising in inguinal endometriosis. Obstet Gynecol. 2006;108:753-755.
26. Shetty M, Lal N, Vu NH. Mullerian adenosarcoma of the ovary: case report and review of the literature. Ultrasound Q. 2007;23:189-191.
27. Manipadam MT, Munemane A, Emmanuel P, McCluggage WG. Ovarian adenosarcoma with extensive deciduoid morphology arising in endometriosis: a case report. Int J Gynecol Pathol. 2008;27(3):398-401.
28. Eifel P, Hendrickson M, Ross J, Ballon S, Martinez A, Kempson R. Simultaneous presentation of carcinoma involving the ovary and the uterine corpus. Cancer. 1982;50(1):163-170.
29. Mahoney AD, Waisman J, Zeldis LJ. Adenomyoma: a precursor of extrauterine mullerian adenosarcoma. Arch Pathol Lab Med. 1977;101:579-584.
30. Lauchlan SC. The secondary mullerian system. Obstetrical and Gynecological Survey. 1972;27(3):133-146.
31. Kaku T, SilverberSG, Major FJ, Miller A, Fetter B, Brady MF. Adenosarcoma of the uterus: a gynecologic oncology group clinicopathologic study of 31 cases. Int J Gynecol Pathol. 1992;11(2):75-88.