PATHOLOGICA 2020;112:219-223;
DOI: 10.32074/1591-951X-114

Case Report

Post-radiation Mullerian adenosarcoma with sarcomatous overgrowth: rare presentation of an uncommon malignancy

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Summary
Mullerian adenosarcoma is an uncommon biphasic malignant uterine tumor. It is composed of benign epithelial and malignant stromal elements. We present a case of a 45-year-old woman who presented with post-menopausal bleeding for three months. She had a significant past medical history of pelvic irradiation for squamous carcinoma of cervix 20 years ago. Pathology revealed adenosarcoma with sarcomatous overgrowth. The patient had a recurrence of pure sarcoma three months later and unfortunately succumbed to her disease. The role of radiation in the pathogenesis of adenosarcoma has been uncommonly described compared to its well established role in the development of carcinosarcoma. Our case fulfils the criteria for a radiation induced sarcoma. We review the salient clinical and pathological features of this uncommon lesion highlighting the importance of sarcomatous overgrowth in these lesions and the possible role of radiation in the development of these tumors.

Key words: Mullerian adenosarcoma, Mullerian adenosarcoma with sarcomatous overgrowth, radiation

Received: April 10, 2020
Accepted: May 4, 2020

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Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Mubeen A, Shahid M, Makary R. Post-radiation Mullerian adenosarcoma with sarcomatous overgrowth: rare presentation of an uncommon malignancy. Pathologica 2020;112:219-223. https://doi.org/10.32074/1591-951X-114

Introduction

Mullerian adenosarcoma (MAS) is an uncommon tumor composed of malignant stromal and benign epithelial components. The first description of adenosarcoma was by Clement and Scully [1]. They also proposed the tumor's current name Mullerian adenosarcoma. Since then, more than 200 cases have been described in the literature. It usually affects postmenopausal women, clinically presenting with pelvic pain or vaginal bleeding. A predisposing role of pelvic radiation in the induction of this tumor has been uncommonly described [2], but not well established. MAS have a characteristic microscopic appearance that is best appreciated at low power magnification. The most important morphologic prognostic factors are sarcomatous overgrowth (SO) and myometrial invasion. The usual treatment is hysterectomy with or without adjuvant therapy.

Case report

A 45-year-old woman presented with post-menopausal bleeding for the past three months. She had a history of invasive cervical squamous cell carcinoma treated with radiotherapy 20 years ago. Endometrial curet-

tage was performed; interpretation was challenging because of limited sampling and stromal atypia mimicking radiation change. A possibility of adenosarcoma was suggested. The patient subsequently underwent hysterectomy with bilateral salpingo-oophorectomy.

Gross examination of the uterus revealed a polypoid tumor (4x2x2cm) involving the entire endometrium without gross myometrial invasion. The cervix, bilateral ovaries and fallopian tubes were not involved. Histologic examination revealed the characteristic phyllodes (leaf-like) architecture with compressed slit-like benign glands and characteristic peri-glandular condensation of spindle shaped stromal cells demonstrating marked atypia and pleomorphism. Average mitotic count was 3/10 high power fields (HPF) (ranging from 2/10HPF to 4/10HPF). Myometrial invasion was minimal (0.5 mm). No lymphovascular invasion was identified. High grade pure sarcomatous overgrowth was present in 25% of the sampled tumor and stained diffusely for smooth muscle actin. Figure 1 (A-D) illustrates representative images of the gross and histologic features.

Three months later, the patient presented with a pelvic recurrence that was surgically resected. Histologically, the tumor was purely sarcomatous devoid of epithelial elements and composed of highly pleomorphic and bizarre cells with severe cytologic atypia in a myxoid background with inflammatory cells. Frequent mitoses including atypical mitotic figures were identified (average 3 mitoses/10HPF). Extensive necrosis was

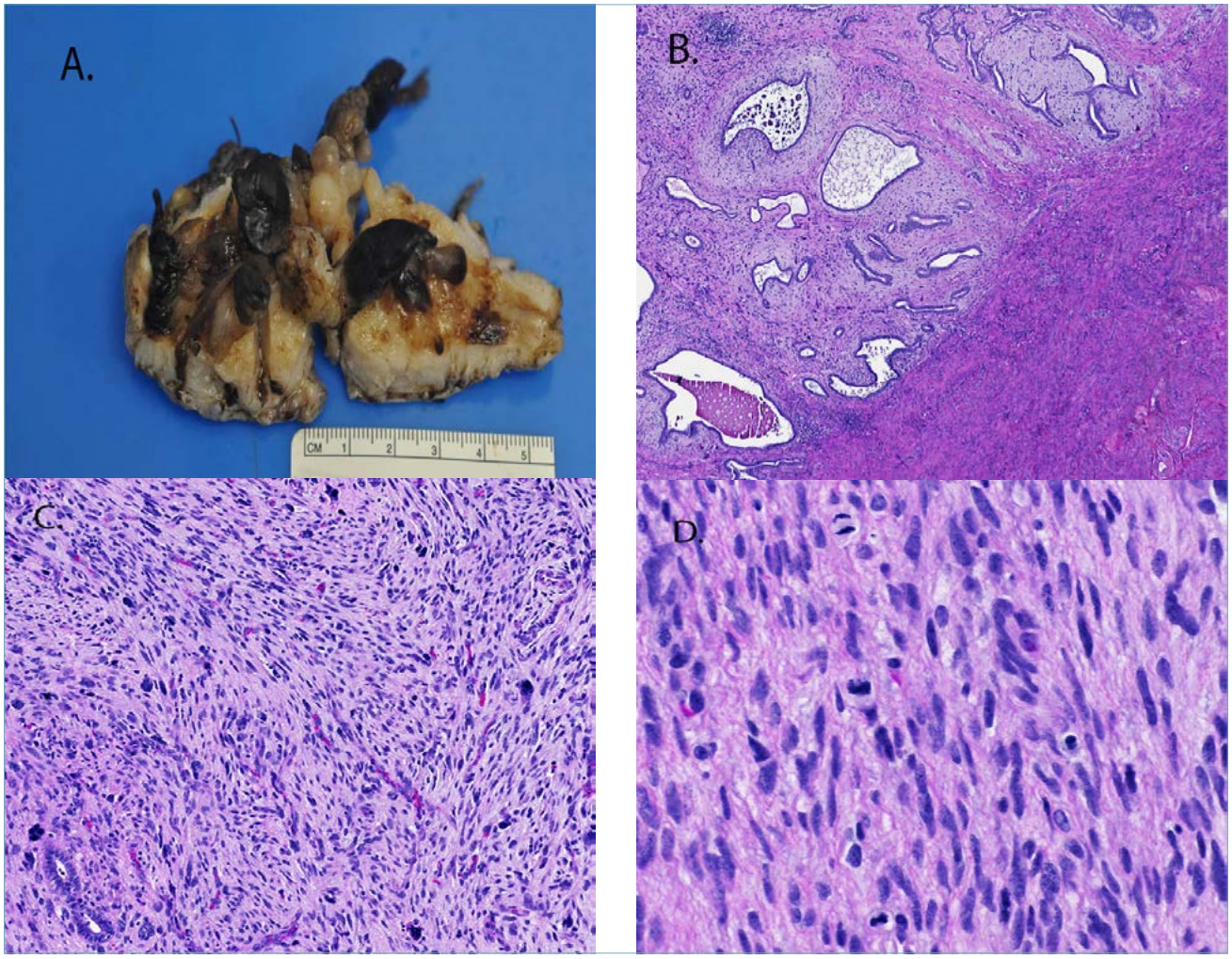

Figure 1. Mullerian adenosarcoma with sarcomatous overgrowth. (A) Gross photo showing polypoid mass filling the entire endometrium. (B) Low power shows characteristic leaf like architecture with peri-glandular cuffing. (C) Area of high grade sarcomatous growth. (D) Stromal atypia and mitoses in the stromal element.

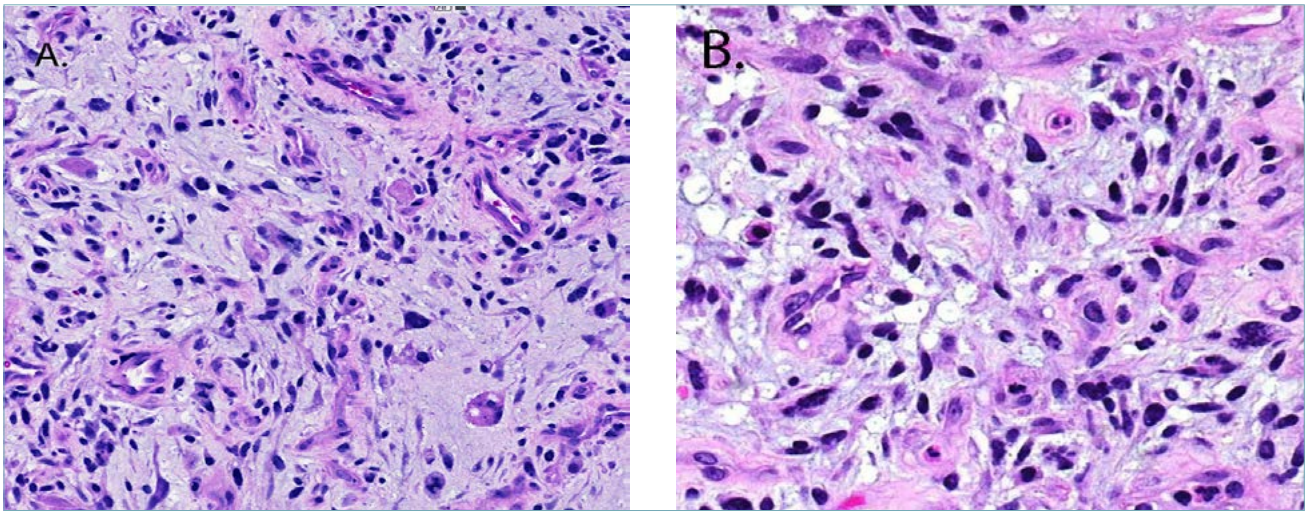

Figure 2. Recurrence of adenosarcoma as pure sarcoma. (A) Atypical stromal cells in a myxoid background, no epithelial elements present. (B) The stromal cells display marked atypia and mitosis.

also present. Figure 2 (A, B) illustrates the histologic features of the recurrence. Unfortunately, the patient succumbed to her illness few months later. She died 10 months from the date of first clinical presentation.

Discussion

MAS are biphasic neoplasms composed of benign epithelial and malignant stromal elements. These tumors occur most commonly in peri- or postmenopausal women (median age 58 years). However, cases have been reported in younger patients including adolescent girls [3]. The most common site is uterus but cases have been described in cervix, ovary, vagina, fallopian tube and extra uterine sites. According to the National Cancer Database, MAS comprise 0.43% of uterine, 0.16% of cervical, and 0.04% of ovarian cancers, respectively [4].

The pathogenesis of these tumors is not clearly understood. Some cases have been linked with tamoxifen therapy for breast cancer [5] and other hyper estrogenic states. The role of radiation has been uncommonly reported in these tumors.

These tumors form polypoid masses filling the endometrial cavity which may project through the cervical os (mean size 5 cm). The cut surface is solid and cystic. Necrosis and hemorrhage may be focally present. Tumors with sarcomatous overgrowth may appear fleshier.

Histologically, the tumor has a distinct low power appearance with a leaf like architecture reminiscent of Phyllodes tumor of the breast. There is also characteristic peri-glandular condensation of stromal elements around the compressed, slit like epithelial glands. These areas are the most atypical and have higher mitoses.

The epithelial element is most commonly endometrioid; metaplastic changes can be present.

The mesenchymal component in a typical MAS is usually a low grade spindle sarcoma. Tumors with sarcomatous overgrowth generally demonstrate high grade atypia; high grade features are, however, not required for diagnosis. Heterologous differentiation like sex cord like differentiation [6] and rhabdomyoblastic differentiation have also been described. Traditionally, the mitotic cut-off for the diagnosis of adenosarcoma was > 2 mitoses/10 HPF. The recent WHO 2014 classification states no mitotic cut off. A diagnosis of MAS can be made with the other characteristic histologic features even in the absence of > 2 mitoses/10 HPF.

Diagnosis on curettings is challenging as the entire spectrum of the lesion may not be present. Recurrent polyps in curettings should raise an alarm for missing a diagnosis of adenosarcoma [7].

The low-grade stromal component is positive for estrogen receptor (ER), progesterone receptor (PR), WT1, smooth muscle actin and CD10. Androgen receptor, desmin and calretinin positivity is less frequent [8]. Cytokeratin (AE1/AE3) is positive in epithelial elements and may rarely be positive in the sarcomatous component. MAS with sarcomatous overgrowth may lose staining with ER, PR, CD10, WT1 and has a higher Ki-67 index [9].

Next-generation DNA sequencing studies have reported TP53 pathway alterations in adenosarcomas with sarcomatous overgrowth [10]. Amplifications of MDM2 and CDK4 and alterations in the PIK3CA/AKT/PTEN pathway have also been reported [11]. A recent study highlights the role of DICER1 mutations in the tumorigenesis of adenosarcomas [12].

The important differential diagnosis for MAS includes adenofibroma, atypical polypoid adenomyoma, polyps with unusual features, polypoid endometriosis, carcinosarcoma, endometrial stromal sarcoma and leiomyosarcoma.

The distinction between adenofibroma and adenosarcoma is controversial with some authors suggesting that adenofibromas may represent well differentiated adenosarcomas. The pattern of immunoreactivity of typical adenosarcomas has been shown to be similar to adenofibroma and other benign entities, thus challenging the existence of adenofibromas [13]. Moreover, some tumors that would fulfil the histologic criteria of adenofibroma have metastases. The distinction is not possible on small biopsies and it has been suggested to use this diagnosis sparingly [8].

Atypical polypoid adenomyoma is a biphasic tumor with a lobular architecture and prominent smooth muscle component. It lacks the leaf-like architecture and periglandular cuffing seen in adenosarcoma.

Endometrial/endocervical polyps can sometimes show atypical features in the form of architectural changes, periglandular stromal alterations and even increased mitoses resembling MAS. These changes, however, are focal compared to MAS. The distinction is very important as the management is significantly different between the two entities [14].

Polypoid endometriosis can superficially resemble adenosarcoma, but usually lacks periglandular stromal cuffing, stromal atypia and intraglandular stromal papillae. The stromal component of MAS may show a striking similarity to low-grade endometrial stromal sarcoma. There is, however, presence of characteristic vasculature, no Phyllodes-like architecture, periglandular cuffing or destructive myometrial invasion.

Carcinosarcoma is composed of malignant epithelial and sarcomatous elements. The epithelium may demonstrate atypia in adenosarcoma, but obvious malignant features are not seen.

MAS are usually treated with hysterectomy with or without salpingo-oophorectomy. Adjuvant chemotherapy or radiotherapy is used in cases with sarcomatous overgrowth.

The prognosis of these tumors is usually good except when the two most important adverse prognostic factors (sarcomatous overgrowth and myometrial invasion) are present. SO is defined as presence of pure sarcomatous overgrowth comprising 25% or more of the tumor volume. The prognostic significance of a lower percentage of sarcomatous overgrowth is not known. Our case exemplifies the aggressive clinical course in MAS with SO even in the absence of significant myometrial invasion.

Previous exposure to radiation is among one of the most commonly associated etiological factors of carcinosarcoma, but its association with MAS is not well elucidated in the literature. The presented case fulfills the criteria for radiation induced sarcoma which are: > 5 years latent period following radiation and different histologic type of tumor in the same field of irradiation. In the original description of 10 cases by Clement and Scully [1], none of the cases had prior history of radiation. In the largest series on 100 cases of MAS, only 5 patients had a history of prior radiation with one patient receiving it for squamous cell carcinoma of the cervix, similar to our case [2].

Recurrences may occur in vagina, pelvis or abdomen and are reported in 20-30% of the patients. Histologically, recurrences are pure sarcomas in majority of cases or less commonly biphasic or even carcinosarcoma [2].

Conclusions

Mullerian adenosarcoma is an uncommon uterine malignancy comprising of benign epithelial and malignant stromal elements. The tumor has characteristic histologic features, but careful examination is needed to differentiate it from other benign and malignant mimickers. Sarcomatous overgrowth and myometrial invasion are important prognostic factors that should be carefully evaluated. Treatment is usually surgical. A role of radiation in the development of these tumors is not fully elucidated and may warrant further investigation.

References

1 Clement PB, Scully RE. Müllerian adenosarcoma of the uterus: a clinicopathologic analysis of ten cases of a distinctive type of müllerian mixed tumor. Cancer 1974;34:1138-49. https://doi.org/10.1002/1097-0142(197410)34:4<1138::aid-cncr2820340425>3.0.co;2-9

2 Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol 1990;21:363-81.

3 Fleming NA, Hopkins L, Nanassy JD, et al. Mullerian adenosarcoma of the cervix in a 10-year-old girl: case report and review of the literature. J Pediatr Adolesc Gynecol 2009;22(4). https://doi.org/10.1155/2012/358302

4 Seagle BLL, Kanis M, Strohl AE, et al. Survival of women with Mullerian adenosarcoma: a National Cancer Data Base study.

Gynecol Oncol 2016;143:636-41. https://doi.org/10.1016/j.ygyno.2016.10.013

5 Clement PB, Oliva E, Young RH. Mullerian Adenosarcoma of the uterine corpus associated with tamoxifen therapy: a report of six cases and a review of tamoxifen-associated endometrial lesions. Int J Gynecol Pathol 1996;15:222-9.

6 Stolnicu S, Balachandran K, Aleykutty MA, et al. Uterine adenosarcomas overgrown by sex-cord-like tumour: report of two cases. J Clin Pathol 2009;62:942-4. https://doi.org/10.1136/jcp.2008.063727

7 Mills SE, Sugg NK, Mahnesmith RC. Endometrial adenosarcoma with pelvic involvement following uterine perforation. Diagn Gynecol Obstet 1981;33149-154. https://doi.org/10.2478/raon-2013-0030

8 Mccluggage WG. A practical approach to the diagnosis of mixed epithelial and mesenchymal tumours of the uterus. Modern Pathology 2015;29:S78-S91. https://doi.org/10.1038/modpathol.2015.137

9 Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. Am J Surg Pathol 2008;32:1013-21. https://doi.org/10.1097/PAS.0b013e318161d1be

10 Hodgson A, Amemiya Y, Seth A, et al. High-grade Müllerian adenosarcoma: genomic and clinicopathologic characterization of a distinct neoplasm with prevalent TP53 pathway alterations and aggressive behavior. Am J Surg Pathol 2017;41:1513-22. https://doi.org/10.1097/pas.0000000000000907

11 Howitt BE, Sholl LM, Dal Cin P, et al. Targeted genomic analysis of mullerian adenosarcoma. J Pathol 2015;235:37-49. https://doi.org/10.1002/path.4442

12 Bean GR, Anderson J, Sangoi AR, et al. DICER1 mutations are frequent in müllerian adenosarcomas and are independent of rhabdomyosarcomatous differentiation. Mod Pathol 2019;32:280-9. https://doi.org/10.1038/s41379-018-0132-5

13 Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. Am J Surg Pathol 2009;33:278-88. https://doi.org/10.1097/PAS.0b013e318181a80d

14 Howitt BE, Quade BJ, Nucci MR. Uterine polyps with features overlapping with those of müllerian adenosarcoma: a clinicopathologic analysis of 29 cases emphasizing their likely benign nature. Am J Surg Pathol 2015;39:116-26. https://doi.org/10.1097/PAS.0000000000000303