Case Report

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Mullerian Adenosarcoma of Uterus and Cervix- A Report of Four Cases with Review of Literature

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ABSTRACT

Uterine sarcomas are rare female genital tract malignancies. Mullerian adenosarcoma is a rare biphasic malignant mesenchymal tumor comprising of a benign glandular and malignant (usually low grade) stromal component, both of which are integral and neoplastic constituents of the tumor.[1] This tumor represents less than 8% of uterine sarcomas. About 200 cases have been reported in the literature so far [2] of which 22 case were from India. Adenosarcomas are usually low grade. Sarcomatous overgrowth is defined as the presence of sarcomatous component is more than 25% of the tumor volume. High grade morphology was termed adenosarcoma with sarcomatous overgrowth (i.e, presence of pure sarcoma , without epithelial component comprising 25% of the tumor).The features of high grade sarcomatous overgrowth include severe nuclear pleomorphism, prominent nucleoli , increased mitotic activity and necrosis[2]. Herein, we present four cases of adenosarcoma of the uterine corpus and cervix, discuss their clinico-pathological findings in detail and add a note on the recent and evolving concepts

Keywords: *Adenosarcoma, Uterus, Sarcoma, Stromal Overgrowth*

Introduction

Uterine sarcomas are rare female genital tract malignancies. Clement and Scully first described mixed tumors of the uterus comprising of malignant stromal component admixed with benign epithelial elements in 1974, [1] following which few more cases were added to their original series in 1979 and the term Mullerian adenosarcoma was recognized universally.[2] Mullerian adenosarcoma is a rare biphasic malignant mesenchymal tumor comprising of a benign glandular and malignant (usually low grade) stromal component, both of which are integral and neoplastic constituents of the tumor. This tumor represents less than 8% of uterine sarcomas.[1] Over the years the spectrum of clinicopathologic findings of adenosarcoma has further expanded thus providing a clear insight about the clinical behavior and morphology of the lesion. About 200 cases have been reported in the literature so far [2] of which 22 cases were from India.

Patients present clinically with complaints of pelvic pain, abnormal vaginal bleeding and in a large percentage of cases with no symptoms. Uterine corpus is the most common site of involvement. Adenosarcoma can also arise in the cervix, fallopian tube, ovary, and vagina. Adenosarcoma that arise outside the female genital tract are most likely due to preexisting endometriosis.

Histopathologically, adenosarcoma are usually low grade. Sarcomatous overgrowth is defined as the presence of a sarcomatous component that is more than 25% of the tumor volume. High grade morphology was termed adenosarcoma with sarcomatous overgrowth (i.e., presence of pure sarcoma, without epithelial component comprising 25% of the tumor). The features of high grade sarcomatous overgrowth include severe nuclear pleomorphism, prominent nucleoli, increased mitotic activity and necrosis [2]. The stromal component may include elements only indigenous to uterus (homologous) or show differentiation towards elements not normally found in the organ (heterologous) such as cartilage, osteoid and striated muscle [1,3]. Some studies suggest the use of tamoxifen may have a role in the pathogenesis of adenosarcoma [2]. Prognosis depends on stage of the tumor, presence of sarcomatous overgrowth and presence of myoinvasion.[3]

Herein, we present four cases of adenosarcoma of the uterine corpus and cervix, discuss their clinico-pathological findings in detail and add a note on the recent and evolving concepts. Ethical clearance obtained from Research department, Apollo Hospital, Chennai

Case Report

Case 1:

A 55-year-old lady was found to have a cervical polyp during her annual health checkup. Cervical smear showed no evidence of intraepithelial lesion or malignancy. A polypectomy was done subsequently. Grossly, the polyp was received in fragments ranging from 0.3 to 2 cm. Histological examination of the cervical polyp showed polypoidal fragments of cervical tissue comprising of dilated and branched glands and broad papillary processes lined by mucinous, endometrioid and tubal type epithelium

underlying cellular stroma with minimal atypia and no lymphovascular invasion or mitosis. (Fig 1a) This was reported as low grade adenosarcoma. Following this the patient underwent total hysterectomy with bilateral salpingo-oophorectomy. There was no residual cervical tumor although associated leiomyoma and adenomyosis were present. Patient is doing well and is on regular follow up for 3 years.

CASE 2:

47-year-old lady with complaints of post coital bleed was found to have a cervical polyp on examination. Grossly the polyp was fragmented with a largest diameter of 2.3 cm. Microscopic examination showed ulcerated cellular lesion composed of sheets of oval to spindle shaped cells with slightly enlarged irregular nuclei with fine chromatin and inconspicuous nucleoli. Mitosis was increased. Amidst the spindle stroma were seen benign glands lined by ciliated columnar epithelium. The morphology was suggestive of adenosarcoma with transition to high grade areas. A completion hysterectomy was advised, however as the biopsy was received from a remote rural centre the patient was lost to follow up.

Case 3:

A 55-year-old woman presented to the gynecology out-patient department with post-menopausal bleeding. Ultrasonography showed thickened endometrium. Endometrial curetting's on pathological examination showed polypoidal fragments of endometrium with loose edematous and myxoid stroma with spindle cells and foci of periglandular stromal condensation. Occasional mitosis was seen. No evidence of stromal atypia was noted. A possibility of well differentiated adenosarcoma versus an adenofibroma was considered. The patient underwent total abdominal hysterectomy with bilateral salpingo oophorectomy and bilateral lymph node dissection. Macroscopic examination revealed polypoidal lesion with focal papillary areas and a soft tissue homogenous nodule measuring 4 × 3 × 2.9cms in the endometrial cavity, infiltrating into the myometrium with a depth of 0.8cms (25%). Microscopic examination showed multiple papillaroidand polypoidal lesions comprising of cystic glands of varying sizes with bland nuclei placed in a fibromatous stroma. (Fig 1b) The largest nodular polyp showed cellular stromal component with polygonal to ovoid cells having eosinophilic to clear cytoplasm and irregular vesicular nuclei with small nucleoli (Fig1 c, d). Amidst this are seen few entrapped endometrial glands. Tumor infiltrated the myometrium superficially. Scattered occasional mitosis were seen. No lymphovascular invasion was identified. The features were consistent with Mullerian adenosarcoma with foci suspicious of sex cord like pattern. IHC was done to exclude de-differentiation. The stromal component was positive for Vimentin and Smooth Muscle Actin. Patchy positivity for p53, Estrogen Receptor (ER) and CD 10 was seen. Ki67 index was shown about 30%. Pan cytokeratin (AE1 + AE3), HMB45, Desmin, Inhibin Alpha, Cyclin D1 were negative (Fig 2a-e). No evidence of de-differentiation was evident. The tumor was designated as Mullerian Adenosarcoma with high grade sarcomatous areas. Additional findings included presence of chronic papillary end cervicitis with blue nevus. The patient was lost to follow up.

Case 4:

A 58-year-old patient presented with complaints of postmenopausal bleeding. Imaging showed thickened and polypoidal endometrium. Hysteroscopic endometrial polypectomy was done. Pathological examination showed a mesenchymal neoplasm with broad fronds composed of plump spindle to epithelioid cells with small prominent nucleoli, enlarged hyperchromatic nuclei, coarse chromatin and scattered many bizarre forms amidst which were seen scattered tubular and dilated benign appearing endometrial glands. (fig3 a-c) The features were suggestive of adenosarcoma with high grade sarcomatous overgrowth. Patient underwent radical hysterectomy with nodal sampling. Endometrial tumor as described above with myometrial invasion of 2mm (Fig 3d) and an incidental focus of endometrial intraepithelial neoplasm (EIN) elsewhere (fig 3 e, f). Adenomyosis was present with a Lymphovascular tumor emboli. Scattered mitotic figures were seen. A diagnosis of adenosarcoma with high-grade sarcomatous areas and associated EIN was made. Patient underwent adjuvant radiotherapy.

Discussion

Mullerian adenosarcomas are uncommon tumors of the female genital tract, commonly occurring in the post-menopausal period, although women of any age group are affected, with the youngest patient being 10 years of age. [2] The general clinical details of the patients in our study are compared in Table 1. The median age ranged from 47 to 58 years, with the mean age being 56 years. [3] Out of the four cases two were in the post-menopausal age group. Endometrium is the common site of these lesion, followed by endocervix and with rare cases reported in the vagina, ovary, fallopian tube and peritoneal surface of the gut, etc. [1-3] The current series included two cases arising from endometrium and cervix each. A rare case of adenosarcoma arising within the myometrium from adenomyosis has also been described in the literature[6]. Tumors that arise in the ovary or extra uterine sites tend to have a higher recurrence rate secondary to lack of a physical barrier to spread within the pelvis and abdomen.[2]

TABLES:

Case	Age	Presenting complaints	Menopause	Site of tumor	Grade	Depth of myometrial invasion	LVI	Mitosis	Associated findings	Stage	Treatment	Status of follow up
1	55	Routine Master health check up	-	Cervix	Low	-	-	-	Leiomyoma and adenomyosis	1a	TAH WTH BSO	NED
2	47	Post coital bleeding	-	Cervix	high	-	-	Increased	-	-	-	Lost to follow up
3	56	Routine master health checkup-thickened endometrium	Menopause	Endometrium	High	0.8cms	-	Scattered	Papillary endo-cervicitis with blue nevus	1b	TAH with BSO with BLND	NED
4	58	Post-menopausal bleeding	Menopause	Endometrial polyp	High	0.2cm	-	Scattered	EIN Adenomyosis-involved by Sarcoma	1b	TAH WITH BSO WITH Radiotherapy	NED

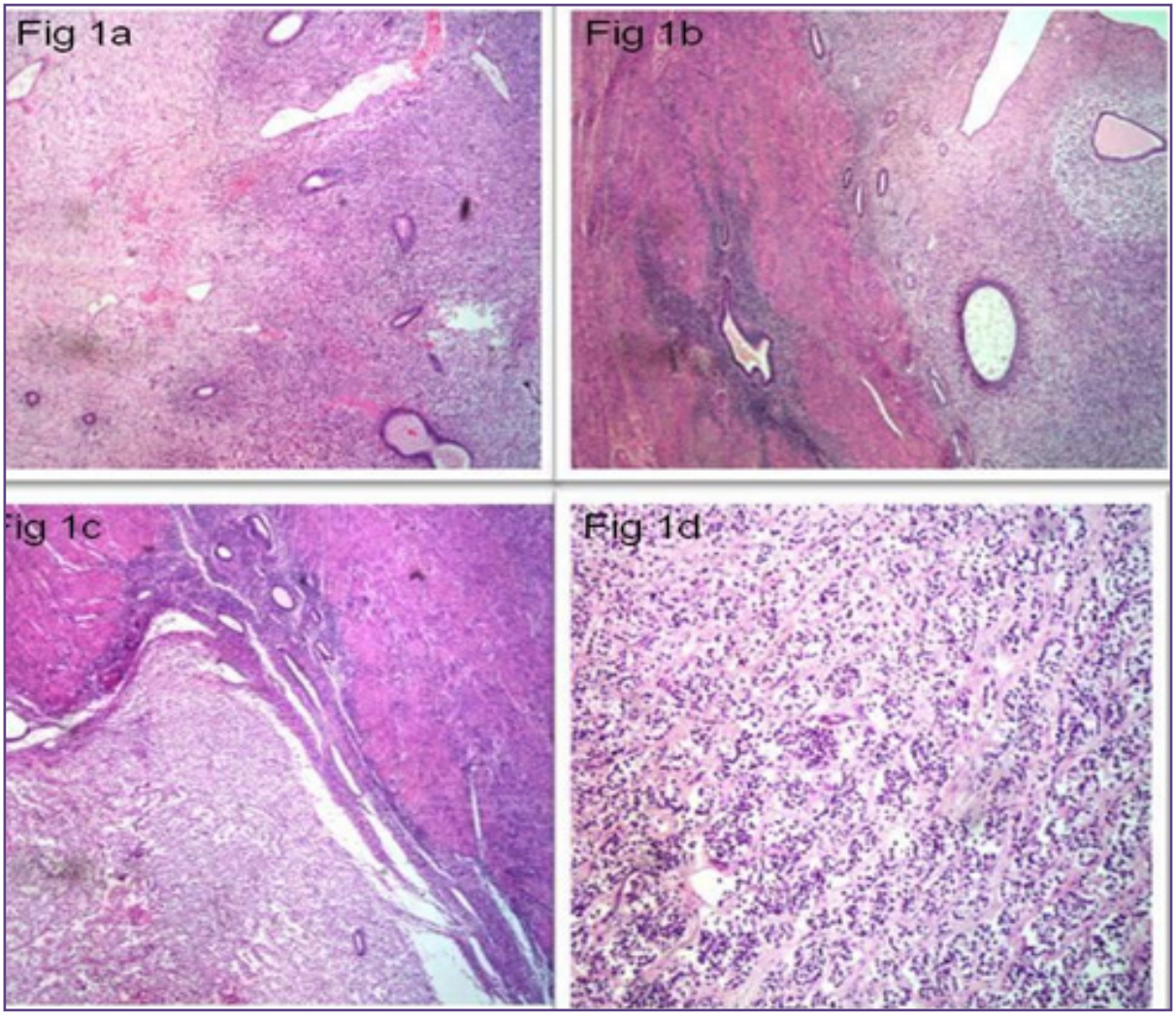

Fig. 1: (a)benign epithelial lining and cellular stroma with spindle cell. (Hematoxylin and eosin, 200x), (b) cystic glands of varying sizes with bland nuclei placed in a fibromatous stroma (hematoxylin and eosin,200x), (c) cellular stromal component with benign endometrial glands and sex cord like differentiation (hematoxylin and eosin, 200x) and (d) polygonal to ovoid cells having eosinophilic to clear cytoplasm and irregular vesicular nuclei with small nucleoli showing sex cord like differentiation (hematoxylin and eosin, 400x).

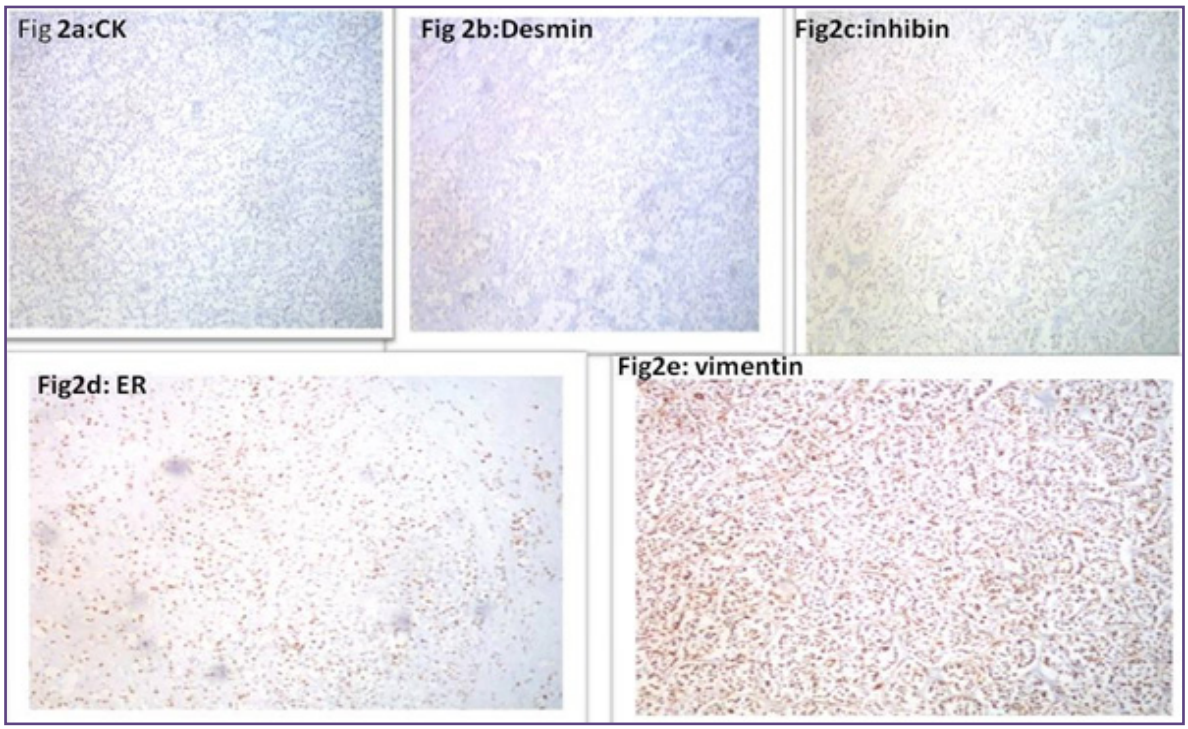

Fig 2: immunohistochemistry (case3): (a) CK negative (diaminobenzidine, 400x), (b) Desmin negative (Diaminobenzidine, 400x), (c) Inhibin negative (diaminobenzidine, 400x) (d) patchy positivity for ER (diaminobenzidine, 400x), (e) Diffuse Vimentin positivity (diaminobenzidine, 400x).

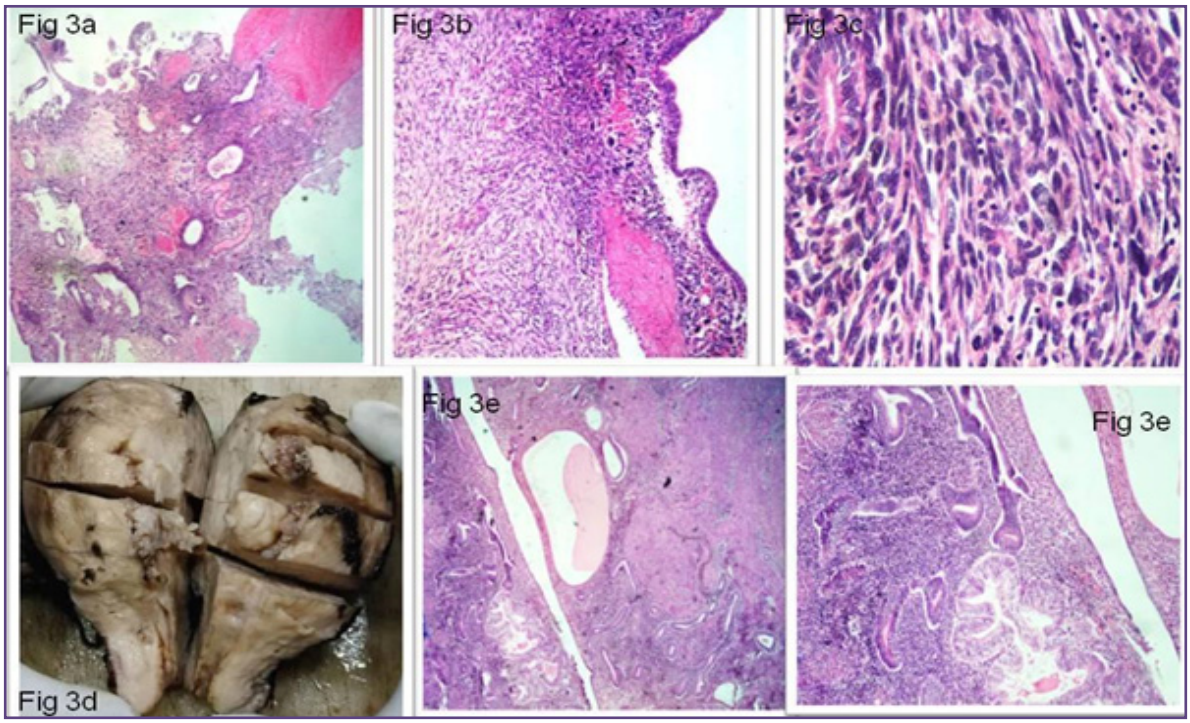

Fig. 3: (a) Benign endometrial glands with cellular spindle cells stroma (H and E, 40x), (b) Benign endometrial glands with high grade sarcomatous area (H and E, 200x), (c) Spindle cells showing marked atypia with mitosis (H and E, 400x) (d) Macroscopy: Polypoidal endometrium involving the entire endometrial cavity. (e & f) focus of Endometrial intraepithelial neoplasm (H and E, 200x).

Myometrial invasion was noted in 58.3% cases of adenosarcomas with stromal overgrowth, in a study done by Rekhi et al [3] which correlated with our study. A study done by Gallardo A et al [2] demonstrated that 36% of adenosarcoma with myometrial invasion recurred, and the risk of recurrence in the absence of myoinvasion was only 7%. Overall survival is around 60% for tumors with myoinvasion and less than 50% for tumors with associated metastasis. A study done by V. Ulker et al [4] demonstrated adenosarcoma with sex cord like pattern in 8 cases which concluded that the presence of sex cord like pattern has better prognosis with no recurrence.[4] One case in our series demonstrated foci suspicious of this pattern which was however, not supported by IHC studies.

The differential diagnoses of adenosarcoma are broad and expands over a spectrum of benign and malignant biphasic tumors. The benign lesions are adenofibroma (which may represent the low-end spectrum of adenosarcoma itself), adenomyoma and atypical polypoidal adenomyoma. Both the glandular and stromal components in these tumours have bland features with rare to no mitoses. Atypical polypoidal adenomyoma exhibits mild epithelial atypia and increased stromal cellularity with no evidence of architectural complexity. When associated with high grade sarcomatous areas the differentials include carcinosarcoma and remotely endometrial stromal sarcoma (ESS), leiomyosarcoma and undifferentiated sarcomas. Carcinosarcoma is a biphasic tumor consisting of malignant epithelial and stromal components with the predominance of the epithelial elements. High grade ESS are positive for cyclin D1 and non-reactive for CD10, ER and PR unlike adenosarcoma. They may have t (7;17) translocation resulting in JAZF1-SUZ12 gene fusion which may differentiate these two lesions in difficult cases.[2]

A small series of cases found that the 2-year progression-free and overall survival rates for tumors with sarcomatous overgrowth was 20% as opposed to 100% for tumors lacking sarcomatous overgrowth.[1] We had one case with associated EIN in our series which has not been described in the literature as yet. Two cases had associated leiomyoma and one case had adenomyosis with adenosarcoma. This possibly indicates hormonal etiology as supported by Rekhi et al [1].

A few molecular alterations have been described in Mullerian adenosarcoma such as hyperdiploid karyotype with multiple structural and numerical abnormalities involving chromosomes 2, 8, 10, 13, 19, and 21; low rates of TP53 mutations; low-level amplification of MDM2 and other genes on band 12q14-15; MYBL1 amplification and ATRX mutation. [2] However, the precise mechanism involved in the Tumorigenesis still remains unclear.

Conclusion

Adenosarcomas of the female genital tract are uncommon tumors with a diverse clinicopathological spectrum. They should be classified into low and high grades. High grade tumors should be accompanied by a comment on the presence/absence of stromal overgrowth and myoinvasion as these indicate a poorer prognosis and warrant aggressive treatment. These tumors should be differentiated from other benign and malignant biphasic neoplasms by histology and other ancillary studies such as IHC and molecular biology wherever applicable. Therapeutically, lymph node sparing TAHBSO is the optimal treatment with adjuvant radiotherapy/chemotherapy in tumors with high malignant potential.

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Competing Interests

None Declared.

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