ORIGINAL ARTICLE

Clinicopathological spectrum of 19 adenosarcomas of female genital tract, including uncommon clinical associations and immunohistochemical profile, reviewed at a single institution

Bharat Rekhi, Kedar K. Deodhar, Amita Maheshwari[1], Santosh Menon, Rajendra Kerkar[1], Jyoti Bajpai[2], Jaya Ghosh[2], Sudeep Gupta[2], Reena Engineer[3], Shyam K. Shrivastava[3]

Departments of Pathology, [1]Surgical Oncology (Gynaecology), [2]Medical Oncology, [3]Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Address for correspondence to:
Dr. Bharat Rekhi, Department of Pathology, Tata Memorial Hospital, Dr E. B. Road, Parel, Mumbai, Maharashtra, India.
E-mail: rekhi.bharat@gmail.com

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ABSTRACT

Background: Adenosarcomas of the female genital tract have been rarely documented as case series from our continent. **Materials and Methods:** Over a seven-year period, 19 adenosarcomas were critically reviewed. **Results:** Nineteen tumors occurred in the age range of 21–65 years (mean: 43), in the endometrium (8), endometrium and cervix (4), cervix (4), and ovary (3). Four cases displayed coexisting leiomyomas; two, adenomyosis; two on background endometriosis; and one in post-treated cervix carcinoma. Histopathologically, the tumors were low grade (10; 52.6%) and high grade (9; 47.3%), the latter with sarcomatous overgrowth (SO) (7/9 cases). Dedifferentiation (8, 42.1%) and conspicuous decidualization (2) were noted. Immunohistochemically, the tumors focally expressed CD10 (4/6), smooth muscle actin (SMA) (3/8), desmin (8/11); diffuse vimentin (7/7), and estrogen receptor/progesterone receptor (ER/PR) (2/4). Ki-67 (6 cases) varied 5–20%. Seventeen patients underwent surgery and four received adjuvant treatment (3/4 high-grade tumors). Five tumors recurred (4 high-grade tumors with SO) and one metastasized. Among 11 patients, five were alive with disease (AWD) (mean: 29.4 months) and six, free of disease (FOD) (mean: 15 months), the latter mostly with low-grade type tumors (83.3% cases). **Conclusions:** Diverse clinicopathological spectrum was noted within adenosarcomas. Low-grade tumors were less aggressive than high-grade ones, with SO. Immunohistochemically, lower CD10 and ER/PR positivity was noted in high-grade tumors. Surgery formed the mainstay of treatment. Adjuvant treatment was offered in high-grade subtypes, including in tumors with SO.

KEY WORDS: Adenosarcoma, mesenchymal tumors of female genital tract, Mullerian adenosarcoma, uterine sarcomas

INTRODUCTION

Müllerian adenosarcoma was first described in the form of a series of 10 cases by Clement and Scully, as a distinct uterine tumor, histopathologically composed of a benign to rarely atypical epithelium and malignant, usually low-grade stromal component.[1] Following this, there have been case reports and case series describing clinicopathological characteristics of this tumor.[2-10] Besides the uterus, adenosarcomas have also been documented at extrauterine sites.[11-18] Over the years, the clinicopathological spectrum of adenosarcomas has further expanded with identification of its association in various clinical settings.[17,19-24] Histopathologically, adenosarcomas are of low and high grades, in certain cases characterized by sarcomatous overgrowth (SO) and they may display heterologous elements including rhabdomyoblastic, osteocartilaginous, and sex cord types.[1,10,13,18,25-27] Recent studies have contributed toward the immunohistochemical analysis of this tumor.[28,29] Lately, Gallardo *et al.*[29] have challenged the existence of an adenofibroma over an adenosarcoma. This concept has been reinforced by Mc Cluggage.[30] Additionally, there are other differential diagnoses that make identification of this tumor challenging at times.

Till date, documentation of a series of adenosarcomas from our continent has been rare, including none from within our country.[31] Herein, we present a clinicopathological spectrum of 19 adenosarcomas, including immunohistochemical results, various associations, and recent concepts.

MATERIALS AND METHODS

The medical records and case files were searched for diagnosed cases of adenosarcomas involving the female genital tract over a seven-year period. A total of 21 cases were retrieved, of which 19 were included in the study after review by BR, as per diagnostic criteria for uterine and ovarian adenosarcomas, including low- and high-grade subtypes with/without SO.[1,10,18,29] The tumors were staged according to the International Federation for Gynecology and Obstetrics (FIGO) staging for uterine sarcomas and ovarian carcinomas in respective cases.[32,33] Two excluded cases were a leiomyosarcoma and a malignant mixed Mullerian tumor (MMMT), respectively. Clinical details were obtained from the case files and electronic medical records across hospital information systems. The diagnostic material was in the form of 'in-house' resection specimens (10; 52.6%), biopsies (2; 10.5%), and paraffin blocks from hysterectomy specimens from referring hospitals (7; 36.8%).

Conventional H&E-stained (H&E: hematoxylin and eosin) microsections were available in all the 19 cases. The number of tumor sections evaluated per case varied from 1 to 20, with an average of 7.4 tumor sections per case. Immunohistochemistry (IHC) was performed by polymer technique (Dako REAL Envision detection system, Glostrup, Denmark), including peroxidase/3′- 3′diaminobenzidine tetrahydrochloride (DAB). Various antibody markers are enlisted in Table 1. Immunohistochemical results were available for 16 (84.2%) tumors.

Clinical outcomes were calculated in months from diagnosis to the last follow-up.

RESULTS

Nineteen adenosarcomas occurred in women in the age range of 21–65 years (mean: 43, median: 43). The commonest complaint was bleeding *per vaginam*. Three cases presented as polypoid lesions, including an incidental tumor. Site wise, most tumors occurred in the uterine endometrium (8; 42.1%), followed by endometrium and cervix (4; 21%), cervix (4; 21%), and ovary (3; 15.7%). Four cases had associated leiomyomas (cases 4, 9, 15, and 18). Two tumors (cases 7 and 11) developed on the background of endometriosis with a medical history of treatment for endometriosis and infertility, two displayed coexisting adenomyosis (cases 14 and 18), and a single tumor (case 8) developed after 20 years in a post-treated (radiotherapy) case of cervix carcinoma stage IB. At that time, this patient was treated with radical radiotherapy (RT), including external RT (4000 cGy ×20 fractions for 35 days) to the pelvis anteroposterior-posteroanterior (AP-PA) portals and intracavitary RT (3000 cGy ×2 fractions). Tumor size in nine cases varied from 3 to 15 cm (mean: 7.4). Six (31.5%) tumors were stage IB, five (26.3%) stage IA, four (21%) stage IC, two (10.5%) tumors were stage IIB and IIIB, respectively. Grossly (7 cases), the most common appearance was cystic, uni or multi, with soft to firm gray-white to yellow cut surfaces. Although three tumors (cases 5, 8, and 13) appeared as polyps involving the lower uterine segment, a single tumor (case 19) was in the form of a 'bulky' proliferative cervical lesion.

On histopathology, common features were irregular dilatation of glands, periglandular cuffing, followed by stromal indentation by glands forming leaf-like/phyllodes-like appearance. The epithelium was endometrioid in most tumors, followed by cuboidal with apical snouts and squamous, ciliated columnar and secretory type in a single tumor, each , respectively. Ten (52.6%) tumors were low grade and nine (47.3%) were high grade with SO in 7/9 tumors. Mitotic counts varied from 2 to 20/10 high power fields (hpf). Seven (58.3%) of 12 tumors, where myometrial invasion was evaluated, displayed invasion, including six (85.7%) high-grade tumors with five tumors revealing SO. A single case showed lymphovascular invasion (case 9). Resected lymph nodes were evaluated in six cases that were free of tumor. Dedifferentiation was noted in eight (42.1%) tumors (cases 1, 2, 5, 9, 10, 12, 14, 17), including rhabdomyoblastic (6), cartilaginous (2), and adipocytic (1) type. A single tumor displayed sex cord elements. These eight cases included more high-grade (6) than low-grade (2) types. Prominent decidualization was noted in two tumors (cases 7 and 11). On IHC, tumor cells expressed CD10 (4/6), SMA (3/8), and CD34 (1/3) focally, vimentin (7/7) diffusely, and desmin (8/11) variably, the latter mostly in rhabdomyoblasts, wherever present as heterologous elements. Ki-67 (6 cases) varied from 5 to 30%. Ki-67 up to 10% was noted in three low-grade tumors and 15–30% counts in two high-grade adenosarcomas. Staining for estrogen receptor (ER) and progesterone receptor (PR) in the stromal component was positive in two tumors and negative in two tumors. Between these, PR was more diffuse than ER. Staining for myogenin was positive in a single tumor (case 12)

Table 1: List of various antibody markers in the present study

Antibody marker	*Clonality, clone*	*Dilution*	*Antigen retrieval*	*Manufacturer*
Vimentin	Monoclonal, V9	1:400	Heat (Tris-EDTA) microwave	Dako, Produkionsveg, Glostrup, Denmark
CD10	Monoclonal, 56C6	1:50	Heat (Tris-EDTA) Pascal	Biocare, PA, USA
Smooth muscle actin (SMA)	Monoclonal, IA4	1:300	Enzymatic (pepsin)	Dako
Desmin	Monoclonal, D33	1:200	Heat (Tris-EDTA) Pascal	Dako
CD34	Monoclonal, QBEnd 10	1:100	Heat (Tris-EDTA) Pascal	Dako
Myogenin	Monoclonal, MyF4	1:50	Heat (sodium citrate) pressure cooker	Novocastra, UK
Ki-67	Monoclonal, MIB1	1:200	Heat (Tris-EDTA) microwave	Dako
Estrogen receptor (ER)	Monoclonal, SP1	1:100	Heat (sodium citrate) pressure cooker	Dako
Progesterone receptor (PR)	Monoclonal, Pgr636	1:100	Heat (sodium citrate) pressure cooker	Dako

to reinforce rhabdomyoblastic differentiation [Figures 1a-g, Figures 2 a-f, Figures 3a-h].

Therapeutically, all 17 patients, with available treatment details, underwent surgery, mostly, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) (11; 64.7%); followed by cystectomy (4; 23.5%) and total abdominal hysterectomy (2; 11.7%). In six cases, lymphadenectomy was performed. Four cases received adjuvant treatment, including chemotherapy (CT) plus RT (3) and CT (1), respectively. The former three cases had high-grade tumors, whereas the latter was of low-grade type. A single case (case 8) of cervical carcinoma received neoadjuvant RT.

Five tumors recurred, of which four were high-grade tumors with SO and one metastasized. Case 1 presented with synchronous tumors in the uterus and pelvis (excluding bilateral adnexae) that were initially completely excised, but recurred in the pelvis after five months. Biopsy confirmed recurrent high-grade sarcoma in the pelvis with resection-positive margins. Among 11 cases with available outcomes (6–82 months, median: 12 months), five were alive with disease (AWD) over 12 to 82 months (mean: 29.4 months) and six were free of disease (FOD) over 6 to 30 months (mean: 13.5 months). Among six cases of FOD over a narrow follow-up, five were of low grade and one was high grade without SO. Among five cases of AWD, three were high grade with SO and two were low grade. Of eight tumors displaying heterologous elements, follow-up details were available in four cases, all of which included cases of AWD and/or with recurrent lesions [Table 2].

DISCUSSION

The present study is the largest documented series of adenosarcomas from our continent. Symptomatology, including bleeding as the commonest symptom, and other presentations like polypoid lesions and abdominal distension, especially in ovarian adenosarcomas, in the present study were noted similarly in earlier studies.[10-12,18]

The mean age of 43 years in this study was in contrast to most western studies, wherein this tumor was predominantly observed in postmenopausal women (mean age: 50–59 years).[10,18,25,29] Kerner *et al*.[12] observed a median age of 39 years. These tumors have also been noted in younger patients, including adolescents, where these are often misdiagnosed.[10,31,34,35] Apart from uterine endometrium that was the commonest site with most IB stage tumors in this study, other sites were cervix, ovary, mesothelium, and intestinal surfaces.[11-18] This wide age range relates to various clinical associations noted with these tumors.[19-21,23,24,36]

Similarly, a wide histopathological spectrum was observed with an almost equal number of low- and high-grade types,

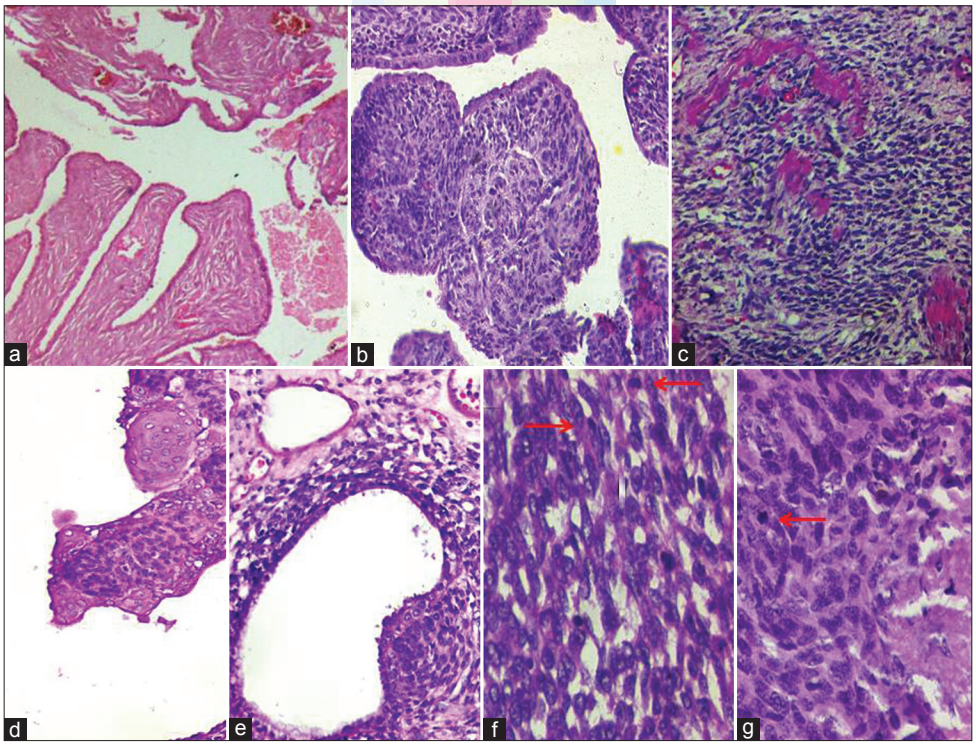

Figure 1: Case 16: Polypoid lesion with benign epithelial lining and spindly, sarcomatous stroma (phyllodes-like) (hematoxylin and eosin, × 40). (b) Case 13: Low-grade sarcomatous stroma with overlying benign cuboidal epithelium (hematoxylin and eosin, × 200). (c) Case 6: Myometrial invasion in a low-grade adenosarcoma (hematoxylin and eosin, × 200). (d) Case 4 (d-f): Squamous metaplasia (hematoxylin and eosin, × 200). (e) Dilated glands with periglandular stromal condensation (hematoxylin and eosin, 200). (f) High-grade sarcomatous differentiation. Mitotic figures (arrows) (hematoxylin and eosin, × 400). (g) Case 3: Sarcomatous overgrowth, including mitosis (arrow) and necrosis (hematoxylin and eosin, × 400)

Table 2: Clinicopathological features of 19 adenosarcomas of female genital tract

Age	Site	Specimen	T-stage	Grade	IHC	Treatment	Outcome
52	Uterus, pelvic wall	SB	IB	High, SO	CD10-, SMA+CD34-	Excision+pelvic mass excision	Rec, AWD (14 mo)
46	Uterus+cervix	SB	IC	High	Desmin+	TAHBSO	NK
55	Uterus+cervix, iliac fossa (right)	Resection	IIIB	High, SO	Vim+, SMA-CD34+	Excision+ Resection (Iliac mass+Sigmoid colon)	Rec, Mets, AWD (82 mo)
40	Uterus+cervix	SB	IA	High	Vim+, Desmin+, ER-, PR-, Ki-67:15%	TAH+CT+RT	FOD (23 mo)
27	Uterus	SB	IC	High, SO	Vim+, SMA- Desmin+ ER+, PR+, Ki-67:20%	TAHBSO+LN + CT+RT	Rec, AWD (12 mo)
35	Cervix	SB	IB	Low	Vim+, CD10+, SMA-Desmin+,	TAHBSO+LN + CT	FOD (6 mo)
30	Ovary	Resection	IIB	Low	Vim+, CD10+, CD34-, ER+, PR+ Ki-67:10%	†TAHBSO	FOD (6 mo)
57	Uterus	Resection	IC	Low	SMA-, Desmin+	NART+TAHBSO+LN	FOD (30 mo)
60	Uterus	SB	IIIB	High, SO	Vim+, Desmin+	TAHBSO+LN	NK
32	Cervix	Resection	IA	Low	NP	TAHBSO	NK
21	Ovary	Resection	IA	Low	Desmin-, Ki-67:10%	¥Cystectomy	FOD (10 mo)
24	Uterus	SB	IB	High, SO	Desmin+, Myogenin+	NK	Rec (NK)
52	Uterus	Resection	IB	Low	Ki-67:5%	TAHBSO+LN+ Omentectomy	AWD (27 mo)
31	Uterus	Resection	IIB	Low	CD10-N, SMA-, Desmin+	TAHBSO	Rec, Mets, AWD (12 mo)
60	Cervix	Bx	IA	Low	Ki-67:10%, SMA+	NK	NK
65	Uterus	Bx	IB	Low	NP	NK	NK
52	Uterus+cervix	Resection	IB	High, SO	Vim+, CD10+, Desmin-ER-, PR-	TAH	On FU
35	Ovary	Resection	IA	Low	NP	TAHBSO+ Omentectomy	FOD (6 mo)
43	Cervix	Resection	IC	High, SO	CD10+, SMA+, Desmin-	TAHBSO+LN+ CT+RT	On FU (3 mo)

SB: Slide and Blocks, Bx: Biopsy, NK: Not Known, T-size: Tumor size in largest dimension, in cm, SO: Sarcomatous overgrowth, IHC: Immunohistochemistry, Vim: Vimentin, SMA: Smooth muscle actin, ER: Estrogen receptor, PR: Progesterone receptor, NP: Not Performed, TAHBSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy, TAH: Total abdominal hysterectomy, LN: Lymph node removed, ¥: Additionally, received treatment for endometriosis, CT: Chemotherapy, RT: Radiotherapy, NART: Neoadjuvant radiotherapy, Rec: Recurrence, Mets: Metastasis, AWD: Alive with disease, FOD: Free of disease, mo: months, FU: On follow-up

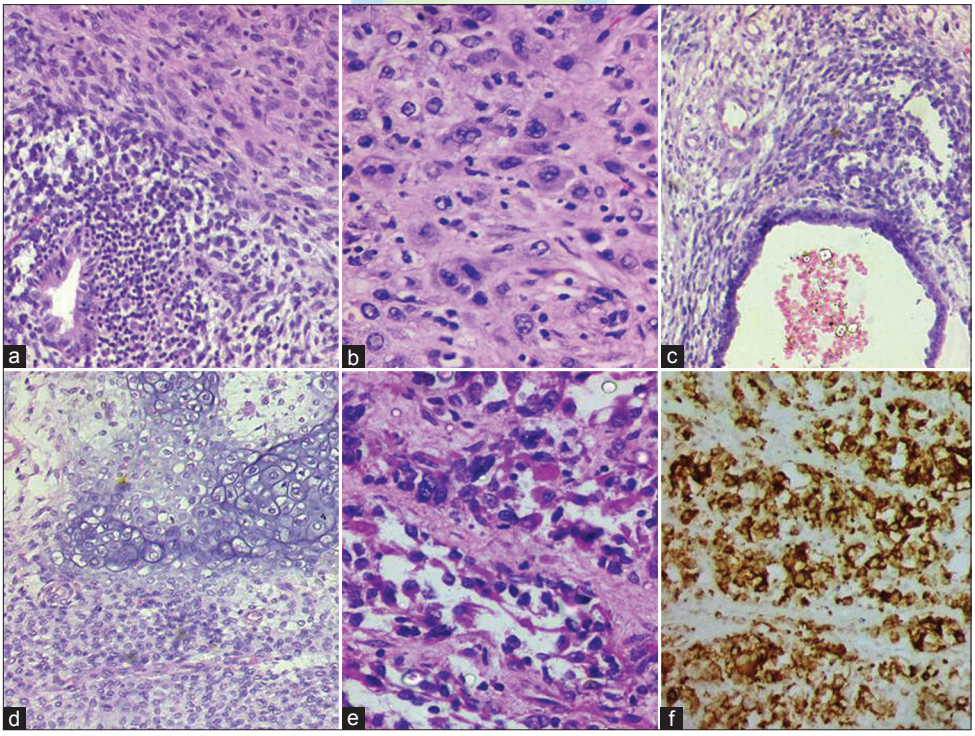

Figure 2: (a) Case 7 (a-b): Glandular and stromal components with decidualization (hematoxylin and eosin, × 200). (b) Decidualization (hematoxylin and eosin, × 400). (c) Case 10 (C-D): Low-grade adenosarcoma (hematoxylin and eosin, 200). (d) Cartilaginous dedifferentiation in a low-grade adenosarcoma (hematoxylin and eosin, × 400). (e) Rhabdomyoblastic dedifferentiation in a high-grade adenosarcoma (hematoxylin and eosin, × 400). (f) Desmin positivity (diaminobenzidine, × 400)

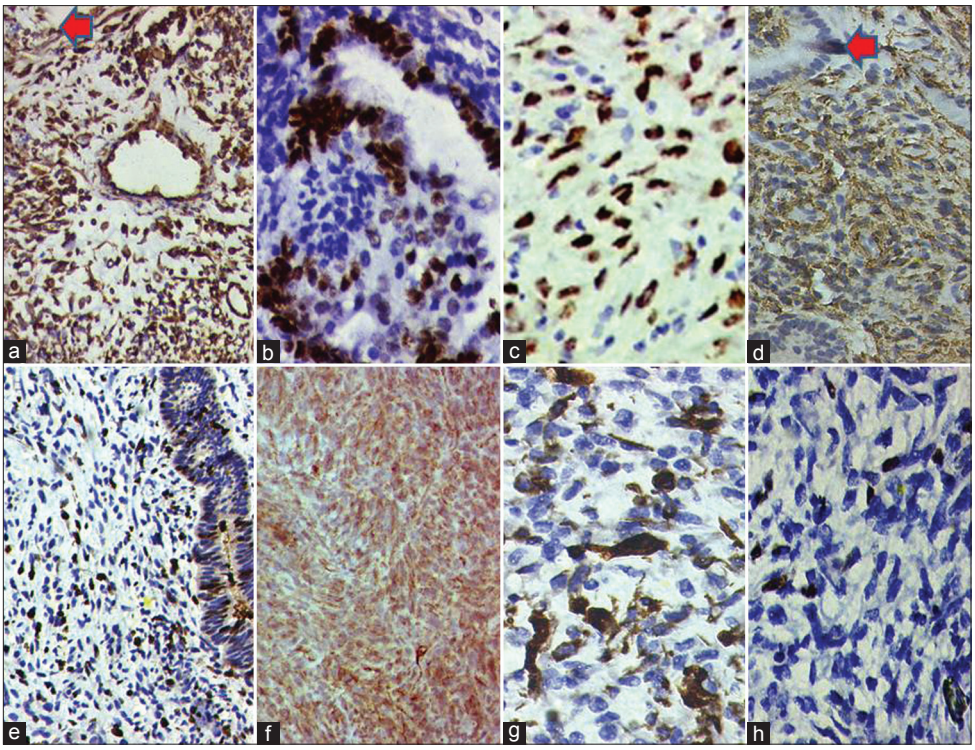

Figure 3: Immunohistochemical results. (a) Case 4 (a-b): Diffuse vimentin positivity, including focal positivity in epithelium (arrow head) (diaminobenzidine × 200). (b) Estrogen receptor-positive glands (diaminobenzidine, × 400). (c) Case 7: Diffuse progesterone receptor positivity in stroma. (diaminobenzidine × 400). (d) Case 15 (d-e): SMA positivity in stroma. Negative glands (arrow head) (diaminobenzidine, × 400). (e) Focal MIB1 positivity (diaminobenzidine, × 400). (f) Case 3: CD34 positivity. (g) Case 12 (g-h): Desmin-positive rhabdomyoblasts (diaminobenzidine, × 400). (h) Discrete myogenin positivity (diaminobenzidine, × 400)

the latter including most tumors with SO.[1,10,18,29] Grossly, the commonest appearance was cystic and variegated, irrespective of site, followed by polypoid in uterine tumors, especially in the lower segment.[10,30] Within the characteristic aforementioned histopathological features, the most commonly observed epithelium was endometrioid type and rarely prominent squamous metaplasia as noted earlier.[7] The other types of epithelium such as mucinous and ciliated, noted in an earlier study[7] were uncommon in the present series. Myometrial invasion was noted in 58.3% tumors, mostly in high-grade types with SO, in contrast to an earlier study documenting the same in 15% tumors.[10] Clement[25] documented 60% cases with SO displaying gross myometrial invasion. The characteristic histopathological features were helpful in sorting out various differential diagnoses, namely adenofibroma, carcinosarcoma/MMMT, endometrial stromal sarcoma (ESS) with glandular proliferation, polypoid adenomyoma, leiomyoma, and other sarcomas.[30] Adenofibroma was ruled out in view of stromal hypercellularity, atypia, and mitotic figures. Existence of an adenofibroma was challenged. Earlier Czernobilsky *et al.*[7] concluded that rather than variable mitotic figures, stromal hypercellularity with atypia and pleomorphism in periglandular and perivascular locations are indicative of an adenosarcoma. Lately, Gallardo *et al.*[29] observed some of their earlier diagnosed adenofibromas based on low mitotic counts, actually behaving as well-differentiated adenosarcomas. McCluggage[30] mentioned that in such dilemmas, one should favor an adenosarcoma that represents a well-differentiated side of the spectrum. At the same time, adequate tumor sampling is vital in such cases. Diagnosis of adenofibroma should be restricted in biopsy samples, considering tumour heterogeneity.

Lack of unequivocal carcinomatous elements ruled out an MMMT. A carcinosarcoma might arise in an adenosarcoma, as was noted in one of the study cases that was finally excluded.[37] Atypical polypoid adenomyoma invariably comprises atypical epithelium with nodules of smooth muscle cells and lacks phyllodes-like pattern in adenosarcomas. ESS, a close differential was ruled out in view of periglandular 'cuffing', absence of periarteriolar arrangement, and lack of irregular 'worm-like' infiltrative pattern in tumors exhibiting myometrial invasion. Phyllodes-like pattern and other common features helped in ruling out other sarcomas, especially rhabdomyosarcoma in cases that exhibited heterologous dedifferentiation, noted in 42.1% tumors. Previous authors identified dedifferentiation in adenosarcomas at various sites ranging from 12.5 to 42.8% in different studies.[10,12,18] Similar to these studies, the commonest heterologous dedifferentiation was rhabdomyoblastic, followed by cartilaginous type, irrespective of tumor grade. The other uncommon variable features were sex cord elements and prominent decidualization, the latter as a result of the intake of antiendometriotic therapy, including progestational drugs. Besides, pregnancy, progesterone-secreting tumors, tumors occurring on the ovarian surface, and idiopathic reasons can lead to prominent decidualization.[38] Association with leiomyomas,

endometriosis, and adenomyosis indicate hormonal etiology of adenosarcomas, at least in a subset of cases.

Immunohistochemically, the most consistently positive marker was vimentin (100%), followed by desmin (72.7%), CD10 (66.6%), SMA (37.5%), ER and PR (50%), and CD34 (33.3%). Earlier, Soslow *et al*.[28] observed positivity of 65% for ER, 76% for PR, 71% for CD10, 67% for SMA, 35% for CD34, 32% for desmin, and 79% positivity for WT-1. Overall IHC profile in the present study overlapped with smooth muscle tumors and ESSs.[30] Therefore, interpretation of IHC markers in uterine mesenchymal tumors should be made as an adjunct to morphological findings. CD10 was diffusely positive in more low-grade tumors. In a larger series, Soslow *et al*.[28] observed lower CD10 positivity in adenosarcomas with SO. ER and PR were expressed in more low-grade tumors than high-grade tumors with SO, as noted earlier.[28] Between the two, PR displayed more diffuse expression. The number of tumors tested for these markers was lesser in our study. In addition, we, like Gallardo *et al*.[29] observed more Ki-67-positive nuclei in high-grade tumors than low-grade tumors.

Treatment for adenosarcomas varies from simple to radical excision, combined with both RT and CT[6,11,18,26,29,33] In this study, 100% cases underwent surgery, irrespective of sites, including TAHBSO for most uterine tumors.[18,29] Simple curettage with RT led to persistence and eventual death in an earlier reported case.[26] Similar to Gallardo *et al*.,[29] lymph nodes removed in certain cases were free of tumor deposits. Adjuvant CT and RT were mostly offered in high-grade tumors. Neoadjuvant RT (NART) was offered in a single low-grade tumor for hemostasis. The role of adjuvant treatment is variable. Although one of two reported cases by Hariri *et al*.[6] died of disease, despite adjuvant RT, a single ovarian adenosarcoma case, documented by Valdez *et al*.,[11] post treatment with CT plus RT survived for nine years.

Among 11 cases with available outcomes (median: 12 months), five were AWD and six were FOD. Most tumor recurrences occurred in high-grade tumors, including those with SO than low-grade type that included more patients FOD, but during a narrow follow-up. Although Martinelli *et al*.[3] concluded that the presence of heterologous elements does not imply a worse outcome, we, like others[12,39] observed heterologous elements, especially rhabdomyoblastic type, more common in high-grade tumors, eventually with a relatively aggressive course. Clement[25] observed death in six of 10 such tumors with SO over nine months to six years.

Site wise, ovarian adenosarcomas have been found to be associated with a grim outcome, because of greater propensity for peritoneal spread.[18] However, the present study, with only three such cases, including all low grade and FOD, has limitations to testify this observation.

CONCLUSIONS

Adenosarcomas are uncommon tumors with diverse clinicopathological spectrum and various cliniciopathological associations. These tumors should be stratified into low and high grades, including with or without SO and myometrial invasion. Heterologous elements, mostly rhabdomyoblastic can be observed irrespective of grade, more so in high-grade tumors. Immunohistochemically, these tumors overlap with ESSs. CD10 and hormone receptor expression is lower in high-grade tumors. Therapeutically, lymph node-sparing TAHBSO is the optimal treatment with role of adjuvant treatment in select cases. A longer follow-up of such cases is important; that was a limitation of this study. Recently, complex karyotype has been identified in a Müllerian adenosarcoma, and this is believed to be vital in the differential diagnosis of Müllerian tumors.[40] Documentation of additional cases of this type would be contributory toward the evolving literature of these tumors, both from the diagnostic and therapeutic aspects.

PRESENTATION

This study was presented (in part) by BR at the 9th Tata Memorial Hospital-Women's Cancer Initiative (TMH-WCI) conference. Recent advances in Breast Cancer and Cancers of Uterine Corpus, 16th October 2011.

This study is accepted for poster presentation by BR at the European Congress of Pathology, 8th-12th Sept 2012, Prague, Czech Republic.

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