Immunohistochemical Markers and the Clinical Course of Adenosarcoma: a Series of Seven Cases

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Abstract

Background: Uterine adenosarcoma, a rare subtype of uterine tumor, is a biphasic tumor consisting of epithelial and mesenchymal elements. There is no research comparing histopathological features of primary and recurrent tumors, including immunohistochemistry; furthermore, the relationship between pathology and the clinical course is unclear. We reviewed the pathology and immunohistochemical features of 7 adenosarcoma cases and investigated the relevance of the histomorphological features to the clinical course. We also compared immunohistochemical features of primary and recurrent tumors.

Methods: Seven patients with adenosarcoma who underwent surgery in our hospital were evaluated. We performed immunohistochemical staining for the estrogen receptor (ER), progesterone receptor (PR), p53, and two SWI/SNF chromatin-remodeling proteins (SMARCA4, BCOR), which were recently developed for the diagnosis of undifferentiated sarcomas in addition to conventional staining methods.

Results: All patients were International Federation of Gynecology and Obstetrics stage 1B to 1C. All tumors were polypoid, and every patient presented with abnormal uterine bleeding. Six patients were over 50 years old and were menopausal; 1 patient was under 50 years old and was non-menopausal (average age 59.1 years). Histologically, the sarcomatous components were homologous in 6 patients and heterogeneous in 1 patient. Four patients were recurrent patients; 3 were non-recurrent. All 4 recurrent patients showed high-grade morphology with sarcomatous overgrowth and were negative for ER and PR. Three recurrences could be evaluated by imaging, showing recurrence only in a distant area; biopsy specimens from these tissues revealed the identical mesenchymal component found in the primary tumor without a benign epithelial component. Immunohistochemical staining results were also the same as for the original tumor, except for the p53 expression in 1 patient. At the primary site, p53 was overexpressed in 2 recurrent patients and had a wild-type level in 1 recurrent patient; however, all 3 recurrent tissues showed overexpression of p53. None of the 7 cases showed SMARCA4 loss, and BCOR expression was positive in 1 case.

Conclusions: Initial pathological analysis of the adenosarcoma with appropriate immunohistochemical staining is vital for prognostic assessment. Expression of p53 might increase at recurrence. SMARCA4 and BCOR could be an index of malignancy, regardless of sarcomatous overgrowth.

Background

Adenosarcomas are tumors of low malignant potential, consisting of benign epithelial and malignant mesenchymal components. They are a rare subtype of uterine tumor, which represents less than 0.2% of uterine malignancies and 10% of carcinosarcomas. Median age at diagnosis is in the 50s, typically postmenopausal women, but also occurs in adolescents to seniors, with age ranging from 13–94 years [1]. Since they are rare, the pathology and immunohistochemical staining methods used for diagnosis and prognostic prediction are limited. Pathologically, in some cases accompanied with sarcomatous overgrowth, deep myometrial invasion, extraterine invasion, and/or heterogenous element, they have poor prognoses [2–5]. Similar to an endometrial stromal sarcoma, immunohistochemical staining of the sarcoma components are highly positive for CD10, WT1, estrogen receptor (ER), and progesterone receptor (PR). In cases with sarcomatous overgrowth, the expression of the markers generally decreases, reflecting the dedifferentiation of the mesenchymal component [6, 7]. TP53 pathway alterations are frequently found in high-grade adenosarcomas, resulting in nuclear atypia and severe pleomorphism identifiable at low-power magnification. Expression of the p53 protein, detected by immunohistochemistry, is highly correlated with mutation status. High-grade adenosarcomas with p53 protein overexpression or loss of expression are aggressive tumors with short-interval recurrences and metastases, regardless of sarcomatous overgrowth [8]. Genetic alterations in the SWI/SNF chromatin remodeling complex components, such as SMARCA4 [9] and BCOR [10, 11], are recently reported in young high-grade uterine sarcomas, but their relationship with adenosarcomas is unknown. We reviewed the pathology and immunohistochemical features of 7 adenosarcoma cases and investigated the relevance of the histomorphological features to the clinical course. In addition, we compared the immunohistochemical features of primary tumors and recurrent tumors; to our knowledge, our study would be the first report on this comparison.

Material And Methods

Case selection

We identified patients diagnosed pathologically with uterine adenosarcoma who were treated in our institute between the years 1992–2017. The specimen data and available clinical information were included.

The following clinical features were recorded: age at diagnosis, menopausal or not, symptoms, type of surgery, adjuvant chemotherapy, recurrence, site of recurrence, treatment after recurrence, follow-up period, and status at last known visit. The following pathologic variables were recorded: International Federation of Gynecology and Obstetrics (FIGO) stage, presence of lymphovascular space invasion, mitotic activity, sarcomatous component (homologous/heterogenous), presence of sarcomatous overgrowth, and depth of myometrial invasion. Sarcomatous overgrowth was defined as when the sarcomatous component occupies more than 25% of the tumor volume. High-grade morphology was defined as a sarcoma with severe nuclear pleomorphism, prominent nucleoli, increased number of mitoses, and necrosis. The institutional review board of the Cancer Institute hospital of JFCR approved this study (IRB approval No.). Informed consent was not required for this retrospective study.

Immunohistochemistry

Primary antibodies and their dilutions are shown in Table 1. Cytoplasmic staining was considered positive for cytokeratin, desmin, SMA, CD10, CD34, and HHF34. Nuclear staining more than 50% was considered positive for ER, PR, MIB-1, cyclin D1, S100, SMARCA4, and BCOR. For p53, complete loss was considered null (mutant type), focal nuclear expression was considered normal (wild type), and nuclear expression in greater than 90% of the tumor cell population was considered overexpression (mutant type).
Table 1
Primary antibodies and their dilutions

| Antibody | Clone | Dilution | Supplier |
|----------|-------|----------|----------|
| Cytokeratin | AE1 and AE3 | 1:200 | Leica |
| CD34 | NU-4A1 | 1:5 | Nichirei |
| Desmin | DE-R-11 | 1:1000 | Leica |
| SMA | 1A4 | 1:1000 | Dako |
| CD10 | 56C6 | 1:100 | Leica |
| Ki-67 | Mib-1 | 1:200 | Dako |
| ER | SP1 | Ready to use | VENTANA (Roche) |
| PR | IE2 | Ready to use | VENTANA (Roche) |
| SMARCA4 | ERP3921 | 1:50 | Abcam, Cambridge, MA, USA |
| S100 | Polyclonal | 1:1000 | Leica |
| Cyclin D1 | P2D11F11 | 1:20 | Leica |
| BCOR | C-10 | 1:100 | SANTA CROZ |
| HHF35 | HHF35 | 1:500 | Enzo |
| p53 | DO-7 | 1:500 | Dako |

SMA: smooth muscle antibody, ER: estrogen receptor, PR: progesterone receptor

Results

General clinical features of the patients (Table 2).

Table 2
Clinical features of the Mullerian adenosarcomas

| Case | Age (years) | Menopause | Macroscopic findings | FIGO stage | Surgery | Adjuvant therapy | PFS (month) | Site of recurrence | OS (month) | Status at last follow |
|------|-------------|-----------|---------------------|------------|---------|-----------------|-------------|--------------------|------------|---------------------|
| Recurrent cases | | | | | | | | | | |
| 1 | 50 | Menopause | Polypoid | C | mRH + BSO | IEP | 6 | Retropertitoneal tissue | 7 | DOD |
| 2 | 57 | Menopause | Polypoid | B | mRH + BSO + PLA + PALA | - | 71 | Lung, Bone | 73 | DOD |
| 3 | 66 | Menopause | Polypoid | B | TAH + BSO + PLA + PALA | - | 12 | Lung | 31 | Death of other disease (SAH) |
| 4 | 65 | Menopause | Polypoid | C | TAH + BSO | - | 10 | Unknown site | 10 | AWD |
| Non-recurrent cases | | | | | | | | | | |
| □ | 75 | Menopause | Polypoid | B | TAH + BSO | 5FU | 2 | - | 2 | NED |
| □ | 58 | Menopause | Polypoid | B | mRH + BSO + PLA + PALA | 5FU | 110 | - | 110 | NED |
| □ | 43 | No | Polypoid | C | TAH + BSO + PLA | IAP | 114 | - | 114 | NED |

AWD: alive with disease, BSO: bilateral salpingo-oophorectomy, DOD: death of disease, IAP: ifosfamide and doxorubicin and cisplatin, IEP: ifosfamide and epirubicin and cisplatin, 5-FU: 5-furouracil, mRH: modified radical hysterectomy, NED: no evidence of disease, OS: overall survival, PALA: paraaortic lymphadnectomy, PFS: progression-free survival, PLA: pelvic lymphadnectomy, SAH: subarachnoid hemorrhage, TAH: total abdominal hysterectomy

The average age at diagnosis was 59.1 years (range, 43–75 years). Six patients were menopausal. The follow-up period ranged from 2–114 months. All 7 cases showed polypoid growth inside the uterine cavity, accompanied with abnormal bleeding. All patients had FIGO stage I disease with myometrial invasion; 4 had stage IB, and 3 had stage IC. Three patients received a hysterectomy and bilateral oophorectomy, and 3 patients received an additional lymphadenectomy. Four patients underwent chemotherapy as adjuvant therapy. Four patients experienced recurrence, after 6, 10, 12, and 71 months after primary surgery. Three patients had only distant recurrence, and 1 patient had an unknown site of recurrence. Two patients died soon after recurrence (1 and 2 months); 1 patient with pulmonary metastasis was cured, but died of another disease; 1 patient transferred to other hospital at recurrence.
**Pathological features and immunohistochemical stains (Tables 3 and 4).**

**Table 3**  
Pathological features and immunohistochemical staining (primary sites)

| Case | FIGO stage | LVSI (Ly V) | Grade | Mytosis /10 HPF | Sarcomatous component | SO | Myoinvasion | SMARCA4 | BCOR | ER | PR | CD10 | p53 | MIB-1 (%) | Cycl D1 |
|------|-------------|-------------|-------|----------------|----------------------|----|--------------|---------|------|----|-----|------|-----|-----------|--------|
|      |             |             |       |                |                      |    |              |         |      |    |     |      |     |           |        |
|      |             |             |       |                |                      |    |              |         |      |    |     |      |     |           |        |
| Recurrent cases | | | | | | | | | | | | | | | | |
| 1    | □C          | ++          | High  | 5               | Homologous           | +  | > 1          | -       | -    | -  | -   | Over expressed | 70   |           |        |
| 2    | □B          | -           | High  | 10–15           | Homologous           | +  | < 1/2        | +       | -    | -  | -   | Normal      | 50   |           |        |
| 3    | □B          | -           | High  | 10              | Homologous           | +  | < 1/2        | -       | -    | +  | -   | Over expressed | 50   | -         |        |
| 4    | □C          | +           | High  | 30              | Heterogenous         | +  | > 1/2        | ND      | -    | ND | -   | Over expressed | ND   | -         |        |
|      |             |             |       |                |                      |    |              |         |      |    |     |      |     |           |        |
| Non-recurrent cases | | | | | | | | | | | | | | | | |
| 5    | □B          | -           | High  | 5               | Homologous           | +  | < 1/2        | +       | -    | -  | -   | Normal      | 30   | □         |        |
| 6    | □B          | -           | Low   | 3               | Homologous           | -  | < 1/2        | -       | +    | +  | -   | Normal      | 5    | -         |        |
| 7    | □C          | -           | Low   | 2               | Homologous           | -  | > 1/2        | ND      | +    | +  | ND  | Null        | ND   | +         |        |

**Table 4**  
Pathological features and immunohistochemical staining (recurrent sites)

| Case | ER | PR | CD10 | p53 | MIB-1(%) | SMA | other |
|------|----|----|------|-----|----------|-----|-------|
| 1    | -  | -  | -    | -   | Over expressed | -  |       |
| 2    | -  | -  | +    | -   | Over expressed | 50 | Desmin(-) HGF35(-) Cytokeratin(-) S100(-) CD34(+)
| 3    | -  | -  | +    | -   | Over expressed | 50 | ND Desmin(+)

**ER:** estrogen receptor, **HPF:** high power field, **LVSI:** lymphovascular invasion, **ND:** not done, **PR:** progesterone receptor, **SMA:** smooth muscle antibody, **SO:** sarcomatous component were homologous in 6 patients, and heterogenous (Fig. 1) in 1 patient. Two patients had lymphovascular space invasion. Five patients, including 4 recurrent patients and 1 non-recurrent patient, had high-grade adenosarcoma with mitosis more than 5/10 HPF, with sarcomatous overgrowth, and were negative for ER and PR. Three recurrent patients had an MIB-1 proliferation index over 50%. In the primary tumor, 2 recurrent patients showed overexpression, and 1 patient showed wild-type expression, of p53; however, all 3 showed overexpression of p53 at the recurrent tissue. None of the patients showed SMARCA4-loss; 1 patient was positive for BCOR (80% of tumor cells).

**Case 6**

showed typical microscopic findings of low-grade adenosarcoma (Fig. 2). Phyllodes-like structure, covered by one layer of benign epithelia with focal mucinous metaplasia, were seen.

**Detailed clinicopathological findings of the recurrent cases**

**Case 1**

The patient was 51-year-old female who visited our hospital for abnormal bleeding. MRI detected a 9 cm tumor filling the uterine cavity and invading through the myometrium. The tumor was diagnosed as sarcoma by biopsy. Hysterectomy and bilateral salpingo-oophorectomy was performed. Macroscopically, a polypoid tumor arising from the uterine fundus extended to the serosa; ascites cytology was positive for malignancy. Microscopically, the highly cellular mesenchymal tumor was covered with benign glandular epithelium similar to intimal surface epithelium and showed leaf-like architecture. Tumor cells were atypical short spindle cells with small round nuclei with mild polymorphism. Some nuclear mitosis was seen (5 mitosis/10 HPF). Tumor necrosis and hemorrhage were present. Lymphovascular space invasions were seen extensively. No heterologous elements were found (Fig. 3).

Immunohistochemical results of the mesenchymal area were negative for ER, PR, CD10, cyclin D1, cytokeratin, BCOR, desmin, SMA, CD34, and S100; p53 was overexpressed; SMARCA4 expression was not lost; and the MIB-1 proliferation index was 70% (Fig. 4).
The patient underwent 6 cycles of adjuvant chemotherapy (IEP: ifosfamide, epirubicin and cisplatin) but recurred in the retroperitoneal cavity 6 months after surgery. Biopsy of the recurrent tumor showed pure sarcoma, the same as the primary tumor without an epithelial component. Immunohistochemical results were negative for ER, PR, CD10, and SMA; p53 was overexpressed; and the MIB-1 proliferation index was 80% (Fig. 5). After 1 cycle of chemotherapy (DG, docetaxel and gemcitabine) the recurrent mass progressed and infiltrated the ureter. The patient died of disease 1 month after the primary surgery.

**Case 2**

The patient was 62-year-old female who presented to our hospital with massive genital bleeding. A large mass was protruding through the cervix, and the patient was diagnosed as sarcoma by biopsy. A hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy were performed. The tumor developed from posterior wall of the uterine corpus, slightly invading the myometrium. There was no lymphovascular space invasion or lymph node metastasis. Microscopically, mostly circular-shaped cells were seen multiplied sparsely around the necrosis tissue. In some areas, brisk mitotic activity, up to 10–15/10 HPF, were found (Fig. 6a, b). These areas were considered sarcomatous overgrowth. The sarcoma component showed non-specific mesenchymal neoplastic features without heterologous elements. Immunohistochemical tests were negative for ER, PR, S100, cytokeratin, HHF35, SMA; positive for SMARCA4, BCOR, and CD10; p53 expression had a wild-type pattern; and the MIB-1 proliferation index was 50%. The patient had recurrence to multiple bones and pulmonary metastasis 6 years after surgery. Biopsy of the iliac bone showed pure sarcoma, the same as the primary tumor without an epithelial component (Fig. 6c). Immunohistochemical tests of the recurrence tumor were the same as the primary tumor, except overexpression of p53. The patient died of disease 2 months after recurrence.

**Case 3**

The patient was 66-year-old female who presented to our hospital with abnormal bleeding and a 9 cm mass partially infiltrated into the uterine myometrium and occupying the uterine cavity. A hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and paraaortic lymphadenectomies were performed. Inside the leaf-like structure covered by one layer of flattened epithelium, cells with a clear cytoplasm constituted a multi-nodular structure (Fig. 6d, e). Immunohistochemical results were negative for ER, PR, cyclin D1, and BCOR; positive for HHF35, SMA, desmin, and SMARCA4; p53 was overexpressed; and the MIB-1 proliferation index was 50%. The sarcomatous component was considered to show leiomyomatous differentiation. No heterologous elements were seen. A 40 mm tumor appeared in the S1 region of right upper lobe one year after surgery. Biopsy of the recurrent tumor showed spindle cells and abundant foam cells comparable with the state after chemotherapy (Fig. 6f). Immunohistochemical tests of the recurrence tumor were the same as the primary tumor. The pulmonary tumor responded to 2 cycles of chemotherapy (IAP: ifosfamide, doxorubicin, and cisplatin) and upper lobe resection was performed; 4 more cycles of chemotherapy were performed after operation. The patient died of a subarachnoid hemorrhage due to rupture of a cerebral aneurysm 5 months after the last chemotherapy treatment.

**Discussion**

All 7 patients were over 40 years old at diagnosis and 6 patients were menopausal. All patients presented with polypoid tumors and abnormal bleeding, and had FIGO stage I disease with myometrium invasion. Four patients experienced recurrence and had sarcomatous overgrowth, with negative ER and PR; 3 patients had high MIB-1 proliferation ratio and overexpression of p53. Three patients had recurrences in distant sites and biopsied tissues were pure sarcoma with the same immunohistochemical staining patterns as the primary tumor; in 1 case p53 expression became significantly stronger in the recurrent tumor as compared with the primary. Two patients with recurrence were not adapted for surgery, progressed rapidly, and died 1–2 months after recurrence.

Adenosarcoma was initially described by Clement and Scully in 1974 [12], who described the tumor as an “admixture of a sarcomatous stromal element resembling endometrial stromal sarcomas of various types and grades and a benign, but often atypical, epithelial component”. The sarcomatous component is usually a low-grade uterine sarcoma, mostly endometrial stromal sarcoma, and the epithelium is often endometrium-like cells. Mixed tumors of epithelial components and mesenchymal components are diagnosed as adenofibroma, adenosarcoma, and carcinosarcoma according to whether each component is benign or malignant. When the sarcomatous component occupies more than 25% of the tumor, it is defined as sarcomatous overgrowth.

Adenosarcomas arise mainly from endometrial lesions (85%), with others arising from the cervix, or being extraterine (e.g., ovary, peritoneum, vagina) [13]. A mass protruding from the external os and occupying the uterine cavity and abnormal vaginal bleeding are the most common symptoms.

Only 2–3% of patients with nodal and/or distant metastases at diagnosis and stage 1 cancer without sarcomatous overgrowth have a good prognosis, which is defined as 5-year overall survival of 80% [13]. However, the following pathological findings are reported to be poor prognostic factors: sarcomatous overgrowth, myometrial invasion, lymphatic and/or vascular invasion, heterologous elements of the sarcomatous component (rhabdomyosarcomatous differentiation), extraperitoneal spread, and an extraterine origin [2–5]. Recurrent intervals were 0.5–9.5 years after primary surgery. About half of the recurrent tumors were pure sarcomas; the others were adenosarcomas. Most of the recurrent tumors (18/21) were typically less well-differentiated than the primary tumors, having non-specific spindle-cell sarcomas, with higher mitotic rates [1].

Our patients’ ages at diagnosis and presentation of polypoid tumor with abnormal bleeding were typical for the clinical course of adenosarcomas. Most recurrences of adenosarcomas occur locally, such as in the vagina and pelvis, and distant metastases are described in about 5% [1]. Our patients had hematogenous recurrence in distant sites; nevertheless, they were all primarily in the early stage. Pathologically, all 4 recurrence patients showed high-grade sarcoma features, such as marked nuclear atypia, coarse chromatin, prominent nucleoli, pleomorphism, weak leaf-like structures, and sarcomatous overgrowth. Immunohistochemical staining showed negative results for ER and PR, high MIB-1 proliferation, and p53 was overexpressed. The findings, taken together, suggest that the 4 cases of recurrent adenosarcomas had sarcoma components with high-grade malignant potential at the onset.
Pathological diagnosis of adenosarcomas is based on the histomorphological observation of the tissue specimens with H&E (hematoxylin and eosin) staining. Because the morphological analyses of adenosarcomas do not always meet typical findings, immunohistochemical tests have also been used. The most common immunohistochemical markers for the sarcomatous component of adenosarcomas are CD10 (71–100%), WT1 (79%), and vimentin (86%) [6, 7]. CD10 positivity is lower in patients with sarcomatous overgrowth [14]. Other markers for adenosarcomas are SMA (50–68%), desmin (32–62.5%), CD34 (35%), and cytokeratin (25–27%). In our study, the primary tumors positive for CD10, SMA, desmin, CD34, and cytokeratin were 3/5, 1/3, 2/5, and 0/2, respectively.

Adenosarcomas frequently express hormone receptors (ER, PR, and androgen receptors) similar to endometrial stromal cells or tumors. However, adenosarcomas with sarcomatous overgrowth lose expression of the hormone receptors, reflecting the nature of dedifferentiation [6, 7, 15]. Tasaka et al. [16] reported an adenosarcoma case arising from endometriosis. The primary tumor was positive for ER and PR, without sarcomatous overgrowth; however, the regrown tumor revealed sarcomatous overgrowth with reduced expression levels of the hormone receptors. Estrogen stimulation such as by tamoxifen [17], pre-existing Stein-Leventhal syndrome [1], or ovarian thecoma [18], may play a role in developing adenosarcoma. There are few cases reporting on hormone therapy [19, 20]; whether hormone receptors are prognostic factors for response to hormone therapy has not been determined yet. Five patients in our study had sarcomatous overgrowth, and all of the patients were negative for ER and PR.

TP53 is a well-known tumor suppressor gene, and the p53 protein expression measured by immunohistochemistry is highly correlated with mutation status. In normal cells, p53 protein stays weakly in a heterogeneous fashion (wild type). In p53-mutated cells, on the other hand, p53 stays strongly in a homogeneous fashion (overexpression) or is completely lost (null pattern). TP53 mutations have been reported only in a small fraction of adenosarcomas. Recently, Hodgson et al. [8], performed comprehensive genomic analysis targeting exons of 409 oncogenes and tumor suppressor genes of 9 high-grade adenosarcomas. High-grade adenosarcomas are frequently associated with TP53 pathway alterations, identified in 7/9 (78%) cases. High-grade adenosarcoma with overexpression of the p53 protein might be aggressive with short-interval recurrences and metastases, regardless of sarcomatous overgrowth.

In our study, 3 recurrent patients showed overexpression of p53 in the primary tumors; 1 recurrent patient showed a wild-type expression pattern, which became overexpressed at recurrence. Recurrent patients, consistent with previous reports. Whether expression of p53 changes at recurrence is unknown.

We also performed SMARCA4 staining, for which none of our case showed loss. Loss of SMARCA4 by immunohistochemistry indicates biallelic inactivation of the SMARCA4 genes [21]. The SMARCA4 gene is one of the tumor-suppressor genes that encode the BRG1 protein, a subunit of the SWI/SNF complex. SMARCA4 loss leads to extremely aggressive malignancy in young patients, such as small cell carcinomas of the ovary, hypercalcemic type [22], and sarcoma of the thorax and central nervous system. Recently genomic studies have identified loss of SMARCA4 in undifferentiated uterine sarcomas and dedifferentiated carcinomas of the endometrium or ovary [9, 23]. However, there have been no reports showing an association between adenosarcomas and SMARCA4-loss. In this research, the positive immunostaining results for SMARCA4 suggest that inactivation of SMARCA4 is not associated with tumorogenesis of adenosarcoma.

BCOR is another SWI/SNF component gene that might affect young high-grade sarcomas, such as clear cell sarcomas of kidney. Marino-Enriquez et al. [11] reported patients 18–32-years-old with 3 high-grade sarcomas with BCOR, regarded as a unique subtype, possibly within the family of endometrial stromal neoplasia. Muthukumarana et al. [10] performed BCOR immunohistochemistry for 13 adenosarcomas and reported that 9 cases expressed BCOR regardless of sarcomatous overgrowth. However, only 1 of these BCOR-positive cases harbored a BCOR gene rearrangement as determined by fluorescent in situ hybridization. In our research, 1 patient was positive for BCOR; however, further analysis of BCOR rearrangements should be performed in adenosarcomas that demonstrate BCOR expression.

The limitations of our study are that the study sample was small and from only a single institute. More multicenter cases and further molecular biology studies are awaited.

### Conclusion

To the best of our knowledge, this is the first adenosarcoma case series comparing microscopic and immunohistochemical findings of primary and recurrent tumors. Most findings that relate to the high-grade malignant potential of the sarcoma component were essentially the same between the primary and recurrent tumors, suggesting that the initial pathological observation of the primary tumor is important for the assessment of the prognosis. Malignant transformation of adenosarcomas might occur through additional mutation of the p53 gene. Molecular testing, including for SMARCA4 and BCOR, might be useful for predicting prognoses of adenosarcomas.

### Abbreviations

- **AWD**: alive with disease, BSO: bilateral salpingo-oophrectomy, DOD: death of disease, ER: estrogen receptor, HPF: high power field, IAP: ifosfamide and doxorubicin and cisplatin, IEP: ifosfamide and epirubicin and cisplatin, 5-FU: 5-fluorouracil, LVSIs: lymphovascular invasion, mRH: modified radical hysterectomy, NED: no evidence of disease, ND: not done, PALA: paraaortic lymphadenectomy, PLA: pelvic lymphadenectomy, PR: progesterone receptor, SAH: subarachnoid hemorrhage, SMA: smooth muscle antibody, SO: sarcomatous overgrowth, TAH: total abdominal hysterectomy

### Declarations
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**Figures**

**Figure 1**

Case 4. H&E staining (original magnification x 400). Rhabdoid tumor cells with eosinophilic cytoplasmic cells.
Figure 2
Case 6. (a) H&E staining (original magnification x 100), (b) H&E staining (original magnification x 400). A phyllodes-like structure composed of mild atypical cells covered by non-atypical epithelial metaplastic cells can be seen. H&E staining is positive for (c) ER and (d) PR (original magnification x 400).
Figure 3

Case 1. (a) Macroscopic findings. A polypoid solid tumor arises from the uterine fundus. The base of the tumor is a white color; the surface layer is amber, which suggests degeneration. (b) H&E staining (original magnification x 40) (c) H&E staining (original magnification x 400). A leaf-like architecture is shown. Atypical short spindle cells show mild polymorphism and comprise the mesenchymal component. It is covered by a benign glandular epithelium, similar to the intimal surface epithelium.
Case 1. (a–j) Immunohistochemical staining is negative for (a) ER, (b) PR, (c) CD10, (d) cyclin D1, (e) cytokeratin, (f) BCOR, and (g) desmin. (h) Overexpressed p53. Staining is positive for (i) SMARCA4 (original magnification x 400). (j) The MIB-1 proliferation index is 70%.
Case 1. (a–d) Recurrent tissue biopsy of the retroperitoneal mass. (a) H&E staining. A mesenchymal component the same as the primary tumor without the epithelial component is seen. (b) ER and (c) PR are negative, and (d) p53 shows overexpression. (e) The MIB-1 proliferation index is 80% (original magnification x 400).
Case 2. Primary site. (a) H&E staining (original magnification x 40) (b) H&E staining (original magnification x 400). Circular shapes or short spindle cells are multiplied sparsely around the necrosis tissue. Brisk mitotic activity and atypical cells are seen. (c) Recurrent site H&E staining in iliac bone biopsy showing the same sarcoma component as the primary site (original magnification x 400). Case 3. Primary site (d) H&E staining (original magnification x 40) (e) H&E staining (original magnification x 400). Inside the leaf-like structure covered by a layer of flattened epithelium, clear cytoplasm cells constitute a multi-nodular structure. (f) Recurrent site H&E staining shows spindle cells and abundant foam cells (original magnification x 400).