

**Uterine Adenosarcoma**

Andre Pinto, MD; Brooke Howitt, MD

- Müllerian adenosarcoma is an uncommon biphasic tumor composed of malignant stromal and benign epithelial components. Morphologically, adenosarcoma is characterized by a broad leaflike architecture, reminiscent of phyllodes tumors of the breast. Periglandular cuffing of the stromal cells around the compressed or cystically dilated glands is characteristic. The mesenchymal component is typically a low-grade spindle cell sarcoma, whereas the epithelial counterpart is commonly endometrioid with frequent squamous or mucinous metaplasia and may, in some circumstances, show mild to moderate atypia. In all cases, it is important to assess for the presence of sarcomatous overgrowth and myometrial invasion, which are the prognostic factors. In this brief review, we present the clinical, histopathologic, and immunohistochemical features of adenosarcoma, as well as updates on the molecular biology of this neoplasm.


In 1974, Clement and Scully reported a series of tumors of the female genital tract that were described as “... mixed tumors of the uterus, in which the stromal component has been malignant, but the epithelial elements, benign,” and proposed naming these tumors *adenosarcoma*. A subsequent study, in 1979, added a few cases to the original series, and the term *Müllerian adenosarcoma* has since become universally recognized. Müllerian adenosarcoma is an uncommon biphasic malignant mesenchymal tumor composed of a benign glandular component and a malignant, but generally low-grade, stromal component. With a growing number of cases reported (now considerably more than 200) in the literature, the spectrum of morphologies and clinical behavior is fairly well understood. The molecular pathogenesis of these tumors, however, remains to be elucidated.

Müllerian adenosarcoma is an uncommon biphasic malignant mesenchymal tumor composed of a benign glandular component and a malignant, but generally low-grade, stromal component. With a growing number of cases reported (now considerably more than 200) in the literature, the spectrum of morphologies and clinical behavior is fairly well understood. The molecular pathogenesis of these tumors, however, remains to be elucidated.

Although uncommon, adenosarcoma affects women of a broad age range. The incidence is highest in perimenopausal women, but cases have been reported in children as young as 10 years. Patients may present clinically with abnormal vaginal bleeding and/or pelvic pain or, in a large percentage of cases, with no symptoms. Although the uterine corpus is by far the most common primary site, adenosarcoma may also arise in the cervix, ovary, fallopian tube, or vagina. Adenosarcoma occurring outside the female genital tract likely represents tumors arising from preexisting endometriosis. Some studies suggest that the use of tamoxifen may have a role in the pathogenesis of adenosarcoma.

The prognosis of adenosarcoma greatly depends on stage and the presence of sarcomatous overgrowth. A small series of cases found that the 2-year progression-free and overall survival rates for tumors with sarcomatous overgrowth were 20% compared with 100% for adenosarcoma lacking sarcomatous overgrowth. Another study 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. Tumors that arise in the ovary or extratubal sites tend to have a higher recurrence rate secondary to lack of a physical barrier to spread within the pelvis and abdomen. A new FIGO (International Federation of Gynecology and Obstetrics) staging system for adenosarcoma, identical to that for endometrial stromal sarcoma (ESS), has been devised recently (Table 1).

**MACROSCOPIC FEATURES**

The uterine cavity is typically filled with an exophytic and polypoid mass, which may project through the cervix. The average size is 5 cm, although tumors up to 50 cm have been reported. The cut surface shows variably cystic and solid areas, and papillary or polypoid projections into cystic spaces can often be appreciated macroscopically (Figure 1). Focal hemorrhage and necrosis may also be present. When sarcomatous overgrowth is present, the mass may acquire a more fleshy appearance commonly seen in other types of sarcoma.

**MICROSCOPIC FEATURES**

Histologically, adenosarcoma is composed of benign-appearing epithelium and malignant stroma. Many of the diagnostic features are best appreciated at low-power magnification and may reflect the gross appearance of this tumor (Figure 2). The architecture often demonstrates a broad leaflike appearance, formed by the malignant stroma compressing the benign epithelium, somewhat resembling a phyllodes tumor of the breast (Figure 3). “Rigid cyst” formation is another architectural pattern in which large, dilated, cystic structures, lined by benign epithelium, are

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surrounded tightly by malignant stroma (Figure 4). Peri-
glandular cuffing of the stromal cells condensing under
the epithelium is characteristic and can also be appreciated from
low-power microscopic examination. The epithelial or
 glandular component is usually endometrioid and frequent-
ly demonstrates metaplasia (squamous and mucinous are
most common) and may show mild to moderate atypia.
The malignant stroma can have a varied appearance but is
classically a low-grade spindle cell sarcoma, frequently with
myxoid foci, with no specific line of differentiation, although
some consider it to resemble ESS. Mitoses are essentially
required for the diagnosis (at least 2 per 10 high-power
fields). The mitoses are usually most pronounced in areas
of periglandular cuffing. Atypical mitotic figures are generally
absent except in the presence of sarcomatous overgrowth. Sex cord-like differen-
tiation can be seen, which has no effect
on prognosis.

Table 1. The FIGO (International Federation of
Gynecology and Obstetrics) Staging System for
Uterine Adenosarcoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor limited to endometrium/endocervix with no myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>≤50% myometrial invasion</td>
</tr>
<tr>
<td>IC</td>
<td>&gt;50% myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the uterus, within the pelvis</td>
</tr>
<tr>
<td>IIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Involvement of other pelvic tissues</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into the abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>&gt;1 site</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Figure 1. Gross image of Müllerian adenosarcoma of the uterus. The mass has a yellow-tan, exophytic appearance, which fills the entire endometrial cavity and extends to the cervix. In this case, sarcomatous overgrowth was present.

Figure 2. Section of endomyometrium showing a large, polypoid mass replacing the endometrium. Note the phyllodes architecture and cleftlike spaces at scanning magnification (hematoxylin-eosin; original magnification ×10).

Figure 3. The resemblance with phyllodes tumor of the breast is evident in a section of adenosarcoma at low power. The leaflike appearance with compressed epithelium is characteristic of these tumors (hematoxylin-eosin; original magnification ×200).

Figure 4. Rigid cyst formation is an architectural pattern also frequently seen in adenosarcoma. Large cystic spaces lined by benign epithelium are surrounded by low-grade malignant stroma (hematoxylin-eosin; original magnification ×200).
The presence or absence of sarcomatous overgrowth is an important prognostic factor and should be assessed in all tumors. Sarcomatous overgrowth is defined as the presence of pure sarcoma (without any epithelial component) comprising at least 25% of the tumor. Morphologic features of sarcomatous overgrowth are typically high grade (Figure 5) and include severe cytologic atypia, brisk mitotic activity, and necrosis; however, high-grade stroma is not a requisite for the diagnosis of sarcomatous overgrowth. When high-grade stroma is present but comprises less than 25% of the tumor, it should be mentioned but no definitive data exist on the prognostic significance. Of course, additional tumor should be sampled and examined histologically if possible. Not uncommonly, adenosarcoma with sarcomatous overgrowth may demonstrate low- to intermediate-grade atypia with a myxoid appearance (Figure 6). Sarcomatous overgrowth is associated with deeper myometrial involvement and lymphovascular invasion. Heterologous elements, most notably rhabdomyoblastic differentiation, have no prognostic significance alone, although they occur most commonly in the presence of sarcomatous overgrowth.

**IMMUNOHISTOCHEMISTRY**

Diffuse or multifocal expression of CD10 in the stromal compartment is seen in most adenosarcomas and often highlights the periglandular cuffing (Figure 7). Immunoreactivity for estrogen and progesterone receptors is also seen in most cases, both in the glandular and stromal components. However, expression of these markers is significantly decreased in adenosarcoma with sarcomatous overgrowth. Mesenchymal markers, such as smooth muscle actin (SMA), desmin, and CD34 can have variable positivity in the stromal component. More than one-half of tumors exhibit expression of SMA and/or desmin, whereas the percentage of CD34 tumors is smaller. Cytokeratins may rarely be focally positive in the sarcomatous component. For an expanded summary of the immunohistochemical profile of adenosarcoma, refer to Table 2.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of adenosarcoma is broad and consists predominantly of tumors that also have a biphasic (epithelial and mesenchymal) appearance. The particular entities considered in the differential diagnosis vary with the type of adenosarcoma. At the very low end of the spectrum, the differential diagnosis includes primarily benign entities, such as the so-called adenofibroma, adenomyoma (benign), endometrial polyps with unusual features, and atypical polypoid adenomyoma. In the presence of high-grade sarcoma and/or sarcomatous overgrowth, the main diagnosis to rule out is carcinosarcoma, although undifferentiated uterine sarcoma, ESS, and leiomyosarcoma should also be considered in the differential diagnosis.

**Differential Diagnosis of Adenosarcoma Without Sarcomatous Overgrowth**

Endometrial polyps, adenofibroma, and adenomyoma are tumors in which both the epithelial and stromal components are morphologically benign. So-called adenofibroma has the architectural features of adenosarcoma, but the stroma is typically hypocellular and fibrotic. Mitoses should be absent or rare. Indeed, adenofibroma may represent the far “low-grade” end of the spectrum of adenosarcoma, and...
thus, a diagnosis of adenofibroma should be rendered with extreme caution, if at all.14,19 Occasionally, benign uterine polyps may display features suggestive of adenosarcoma; however, those features are subdiagnostic, typically subtle, and only partially involve the polyp.23 Endometrial polyps with myomatous stroma can resemble adenosarcoma, but the stromal component is made of smooth muscle cells that form fascicles. Fascular growth of the stromal component in adenosarcoma is unusual. Atypical polypoid adenomyoma is characterized by endometrial glands frequently displaying mild cytologic and architectural atypia and often diffuse or focal squamous morular metaplasia. The myofibromatous stroma is cellular but lacks the leaflike architecture of adenosarcoma.

### Differential Diagnosis of Adenosarcoma With Sarcomatous Overgrowth

Perhaps the most challenging differential diagnosis is carcinosarcoma. As the name implies, both elements of these neoplasms are malignant, but adenosarcoma can demonstrate cytologic atypia in the epithelial component; thus, the distinction from a small carcinoma can be difficult. To further complicate this differential diagnosis, epithelial malignancies may arise in the setting of adenosarcoma, and carcinosarcomas can focally demonstrate areas mimicking adenosarcoma.4 In most carcinosarcomas, the sarcomatous component is not predominant; nevertheless, extensive sampling may be required to distinguish adenosarcoma with sarcomatous overgrowth from carcinosarcomas composed predominantly of sarcoma.

When the tumor cells are markedly high grade and do not recapitulate normal endometrial stroma, undifferentiated uterine sarcoma should be considered. If entrapped glands are present, they can mimic adenosarcoma. These tumors are composed of pleomorphic, undifferentiated, malignant cells with high mitotic index. In the absence of classic features of adenosarcoma, undifferentiated uterine sarcoma should be diagnosed, with the understanding that a subset of these heterogenous tumors may represent extensive sarcomatous overgrowth of an adenosarcoma.

Low-grade ESS may resemble adenosarcoma with sarcomatous overgrowth, particularly if glandular elements and/ or entrapped benign endometrial glands are present. In ESS, the tumor cells are monomorphic and have fusirom, round to ovoid nuclei and fine chromatin. The cell borders are indistinct, and cytoplasm is scant. Delicate vasculature is characteristic of these tumors, which is composed of thin-walled blood vessels surrounded by whorling of tumor cells.

Because CD10 immunostain is positive in both adenosarcoma and ESS, it is not helpful in distinguishing between these tumors. Many ESSs have a t(7;17) translocation resulting in JAZF1-SUZ12 gene fusion, and cytogenetic studies may be used in difficult cases.

A high-grade ESS has also been described,24 which is characterized by malignant cells with uniform atypia and high mitotic index. The immunohistochemical profile varies, but these tumors are generally nonreactive for CD10, estrogen receptor, and progesterone receptor, in contrast to adenosarcoma. High-grade ESSs are positive for cyclin D1, which indirectly reflects the presence of a YWHAE-FAM22 gene fusion product created by the characteristic translocation t(10;17).24

Given its frequency among mesenchymal tumors of the gynecologic tract, leiomyosarcoma may also be considered. Leiomyosarcoma may uncommonly entrap benign endometrial glands but does not demonstrate features characteristic for adenosarcoma. The presence of typical fascicular architecture and immunohistochemical positivity for smooth muscle markers, particularly caldesmon, is diagnostic of leiomyosarcoma.

### Molecular Diagnostics

The precise molecular mechanism of tumorigenesis in adenosarcoma remains unclear. One reported karyotype of adenosarcoma with sarcomatous overgrowth revealed a hyperdiploid karyotype with multiple structural and numerical abnormalities involving chromosomes 2, 8, 10, 13, 19, and 21.25 Some studies have found low rates of TP53 mutations,26–28 and others have described low-level amplification of MDM2 and other genes on band 12q14–15.26,27 Recently described alterations in adenosarcoma include MYBL1 amplification and ATRX mutation, which are each present in 50% of adenosarcomas with sarcomatous overgrowth.27 MYBL1 is a transcription factor that regulates cell proliferation and is amplified in subsets of other types of tumors, including 10% of uterine carcinosarcoma (http://www.cbiportal.org; accessed January 14, 2015). ATRX regulates DNA methylation and chromatin remodeling; loss-of-function mutations in ATRX have prognostic significance in other tumor types.29

### Treatment

Total abdominal or laparoscopic-assisted vaginal hysterectomy is the treatment of choice for uterine adenosarcoma, with or without bilateral salpingo-oophorectomy. One study13 did not identify any ovarian metastases in patients who underwent bilateral salpingo-oophorectomy for uterine adenosarcoma. However, given the frequent positivity of estrogen and progesterone receptors in adenosarcoma, removal of the ovaries could potentially benefit patients, even in the absence of metastatic disease—but that benefit needs to be weighed against the age of the patient and cost of surgical menopause.

There is no standardized chemotherapy, hormonal therapy, or radiation therapy in adenosarcoma, but standard sarcoma chemotherapy regimens, such as doxorubicin, ifosfamide, or gemcitabine/docetaxel, and newer drugs, such as trabectedin, appear to have some efficacy in adenosarcoma with sarcomatous overgrowth.13,30,31

### Conclusion

Müllerian adenosarcoma is a relatively uncommon entity in gynecologic pathology that has distinctive clinical and
histologic characteristics. It is important for pathologists to be aware of the morphologic features of these neoplasms to distinguish them from other biphasic (epithelial and mesenchymal) tumors, both benign and malignant. Adenosarcoma is of generally low malignant potential, except when accompanied by sarcomatous overgrowth and myoinvasion. Patients with adenosarcoma lacking these 2 histopathologic features have an excellent prognosis.

References

CAP16 Abstract Program Submission Dates Announced

Abstract and case study submissions to the College of American Pathologists (CAP) 2016 Abstract Program will be accepted beginning on Friday, January 8 through 5 p.m. Central time Friday, March 11, 2016.

Accepted submissions will appear on the Archives of Pathology & Laboratory Medicine Web site as a Web-only supplement to the September 2016 issue. The CAP16 meeting will be held from September 25 to 28 in Las Vegas, Nevada.

Visit the CAP16 Web site (www.cap.org/cap16) for additional abstract program information as it becomes available.