

## **UTERINE ADENOSARCOMA**

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### **Definition of Adenosarcoma:**

A mixed tumor composed of benign neoplastic glandular elements and sarcomatous, albeit often low-grade, stromal elements.

### **Clinical features:**

Adenosarcoma occurs in all age groups but is most commonly seen in women after the menopause (1). The most common presenting symptom is abnormal vaginal bleeding but some patients present with pelvic pain, an abdominal mass or vaginal discharge. Some patients have taken tamoxifen therapy or have had prior radiation therapy (1,2).

Adenosarcomas more uncommonly have an extrauterine location and involve the ovary, pelvic tissues or intestinal serosa (3).

### **Gross features:**

Adenosarcoma most commonly arises from the endometrium, including the lower uterine segment, but rare cases arise in the endocervix and within the myometrium, probably from adenomyosis. The uterine cavity is typically filled and distended by a coarsely lobulated, soft, spongy or rubbery, polypoid and sometimes large mass which may project through the cervical os. The cut surface may show variably sized cysts or clefts. There is often focal hemorrhage and necrosis. The margin of the tumor is usually clearly defined. Some tumors form multiple polyps.

**Microscopic features:**

The mixed nature of the tumor is exemplified by the presence of both glandular and stromal elements, the latter predominating. An essential feature is an epithelial lining that is well differentiated but neoplastic (described often as “benign”) and a malignant mesenchymal component, thereby placing the tumor halfway along the spectrum of mixed müllerian tumors, with adenofibroma at one end and carcinosarcoma at the other. At low power magnification, the tumor often has a leaf-like pattern, resembling a phyllodes tumor of the breast. The glands are widely separated by the abundant stromal component and are usually lined by cuboidal or low columnar epithelium. In most cases, this epithelium resembles that of proliferative endometrium, although epithelium of ciliated, mucinous and occasionally squamous type may also be seen. Some glands are dilated while others are slit-like. Commonly, the epithelium appears active, showing mitotic activity or subnuclear vacuoles despite the advanced age of some patients, even when the adjacent endometrium is atrophic. Focal glandular crowding and nuclear atypia of the epithelial element is present in some cases, which may amount to atypical hyperplasia. Commonly, some of the epithelial cells will be cuboidal, with a large nucleolus and abundant eosinophilic cytoplasm. Rarely a carcinoma arises within a preexisting adenosarcoma, suggesting this may be the histogenetic origin of a small number of carcinosarcomas (4). The stromal component, which is often low grade, is composed of spindled and/or round cells, the former usually arranged in whorls and the latter loosely dispersed. One of the most characteristic features of adenosarcoma is the manner in which the stromal cells concentrate about the glandular components, forming a cuff (“periglandular cuffing”) or so-called “cambium” layer. This cellular zone, in contrast to the more hyaline or fibrous areas away from the glands, is where the maximum nuclear atypia and mitotic activity is typically found. While a mitotic count of  $\geq 1$  per 10 HPFs is often found in these tumors, it may be less in some. Also within many areas in any individual neoplasm, it may be less. In practice, if the characteristic leaf-like pattern is present with periglandular cuffing, a diagnosis of adenosarcoma is made in the absence of mitotic figures. Intraglandular protrusions of cellular stroma are also a characteristic feature. Most adenosarcomas contain exclusively homologous mesenchymal elements, composed of tissue types that are normally found in the uterus, including non-specific fibroblastic stroma and endometrial stromal sarcoma or

undifferentiated sarcoma. About a quarter of the tumors have heterologous elements with rhabdomyoblasts predominating, but features of chondrosarcoma and liposarcoma may also occur. Sex cord-like elements, identical to those seen in endometrial stromal neoplasms, may be present within the mesenchymal component (5). Occasionally, there is marked decidualisation of the stromal component secondary to hormone usage (6).

Most adenosarcomas are confined to the endometrium. Approximately 15% invade into the myometrium, usually the inner half. Deep invasion is rare in the absence of sarcomatous overgrowth (see below).

#### **Adenosarcoma with sarcomatous overgrowth:**

Adenosarcomas in which more than 25% of the tumor is composed of pure sarcoma are designated as “adenosarcoma with sarcomatous overgrowth” (7). The sarcomatous component is usually composed of more poorly differentiated tumor, resembling undifferentiated sarcoma, with more atypia and a higher mitotic rate than in the sarcomatous element of the residual adenosarcoma.

#### **Immunohistochemistry:**

In most adenosarcomas without sarcomatous overgrowth, the stromal component expresses ER, PR, CD10 and WT1, is negative with p53 and exhibits a low MIB1 proliferation index (8). Thus, the immunophenotype resembles that of an endometrial stromal sarcoma, although often the cellular morphology is more that of non-specific fibroblast-like cells rather than overt endometrial stroma. In cases with sarcomatous overgrowth, the mesenchymal component exhibits a higher MIB1 proliferation, may be p53 positive and there is usually loss of expression of ER, PR and CD10, the immunophenotype being similar to that of an undifferentiated uterine sarcoma (8). In adenosarcomas with sarcomatous overgrowth, the mesenchymal component may be DNA aneuploid while in adenosarcomas without sarcomatous overgrowth, it is usually DNA diploid (9).

**Treatment and Prognosis:**

The treatment of choice is hysterectomy with bilateral salpingo-oophorectomy. The role of adjuvant radiotherapy and chemotherapy is not clear and has not been fully evaluated (10).

Adenosarcoma has a relatively low malignant potential unless associated with sarcomatous overgrowth. Recurrences, which occur in 20-30% of cases, are usually confined to the vagina, pelvis or abdomen. They may be late, for which reason long term follow-up is needed, and are usually composed solely of the mesenchymal element, although occasionally glands are present. Distant metastasis, which occurs in a small percentage of cases, is almost always composed of pure sarcoma (1). Not unexpectedly, myometrial invasion and sarcomatous overgrowth are associated with an increased risk of recurrence. The presence of sarcomatous overgrowth in an adenosarcoma predicts a poor prognosis and may be associated with deep myometrial invasion or distant metastasis (7,8,11).

**Differential diagnosis:**

Adenosarcoma is distinguished from adenofibroma by the presence of a stromal mitotic count of 1 or more per 10 HPF (although as discussed this is not always present), marked stromal cellularity with periglandular cuffing or more than mild nuclear atypia of the stromal cells. As adenosarcoma is much more common than adenofibroma, if in doubt, diagnose low grade adenosarcoma to ensure optimal management, including long-term follow up. At the heart of the controversy whether or not adenofibroma exists as an entity is the ability to distinguish it from adenosarcoma. The critical features are the number of mitotic figures in the stroma, the morphology of the stromal cells and the presence of periglandular cuffing by stromal cells. Mitotic counts greater than 1 per 10 HPFs warrant a diagnosis of müllerian adenosarcoma, a diagnosis that should also be made if there is marked stromal cellularity, more than mild nuclear atypia or periglandular stromal cuffing. Even in the absence of mitoses, cases may recur or rarely metastasise (12). A confident diagnosis of adenofibroma cannot be made on curetted or avulsed material because adenosarcoma cannot be excluded unless the whole tumor is available for examination. Thus, a hysterectomy is required to ensure that the tissue examined was not just the most benign area of an adenosarcoma. Using these strict criteria, the diagnosis of adenofibroma is made only rarely. For practical purposes, this diagnosis cannot be made on a biopsy or curetted specimen. For this reason an argument can easily be made that all adenofibromas are low grade or well differentiated adenosarcomas (12).

Carcinosarcoma contains clearly malignant epithelial elements in addition to the sarcomatous component. The stromal component of most carcinosarcomas is highly pleomorphic and less well differentiated than in most adenosarcomas and lacks the periglandular cuff of increased stromal cellularity that is so characteristic of adenosarcoma. As stated earlier, rarely a carcinoma may arise in a preexisting adenosarcoma.

Benign endometrial polyps lack a leaf-like pattern and have stroma similar to the adjacent endometrium or the stroma may be hyaline or fibrous. There may be mild increased cellularity around the glands but this is rarely a prominent feature. If the stroma of an endometrial polyp is markedly cellular with nuclear atypia and mitotic activity, then adenosarcoma should be considered, particularly if there is significant periglandular cuffing. Rarely, markedly atypical cells of symplastic type occur within the stroma of an endometrial polyp and may result in consideration of an adenosarcoma (13).

Atypical polypoid adenomyoma lacks a leaf-like pattern and is composed of stroma that is predominantly cellular smooth muscle or myofibroblastic and may exhibit some mitotic activity. The epithelial elements usually show greater cytological and architectural atypia than is seen in adenosarcoma and foci of squamous differentiation, in the form of morules which sometimes contain central necrosis, are characteristic.

Endometrial stromal sarcoma may have occasional entrapped endometrial glands at the margin of the tumor and, rarely, endometrioid glandular differentiation may be present within the tumor (14,15). The distribution of these glands, however, differs from that in adenosarcoma and periglandular stromal cuffing is not seen. Endometrial stromal sarcoma usually exhibits widespread irregular myometrial infiltration while most adenosarcomas exhibit little in the way of myometrial invasion unless there is sarcomatous overgrowth. However, areas within endometrial stromal sarcoma with glandular differentiation may be virtually indistinguishable from adenosarcoma (14). Other uterine sarcomas, such as undifferentiated sarcoma, may contain entrapped glands but these are not an integral component of the tumor.

Embryonal rhabdomyosarcoma (sarcoma botryoides), which most commonly occurs as a polypoid mass in the cervix of females in the late teens and early twenties (16), may contain entrapped glands which are surrounded by cuffs of tumor cells, resulting in a cambium layer. This may result in mimicry of an adenosarcoma in which the stromal component exhibits rhabdomyoblastic differentiation. In embryonal rhabdomyosarcoma, the entrapped glands are usually largely confined to the surface and the leaf-like pattern typical of adenosarcoma is absent.

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# MESENCHYMAL TUMOURS OF THE UTERUS- USCAP, 2009

## **ADENOSARCOMA**

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# TO DISCUSS

- definition
- morphological criteria
- more uncommon features
- differential diagnosis
- prognostic features
- behaviour/management

# WHO 2003 DEFINITION

- a neoplasm composed of an admixture of benign epithelial and malignant mesenchymal components
- both should be integral and neoplastic component of neoplasm
- considered as neoplasms of low malignant potential

# MIXED MULLERIAN TUMOURS

## **ADENOFIBROMA**

(benign epithelium and  
benign stroma)

## **CARCINOFIBROMA**

(malignant epithelium and  
benign stroma)

## **ADENOSARCOMA**

(benign epithelium and  
malignant stroma)

## **CARCINOSARCOMA**

(malignant epithelium and  
malignant stroma)

# SITES

- uterine corpus
- uterine cervix
- ovary/peritoneum
- vagina
- extra-genital eg intestine

# CLINICAL PRESENTATION

- most common in postmenopausal age group
- 30% in premenopausal
- usually present with abnormal vaginal bleeding
- occasionally present with uterine mass, abdominal pain or vaginal discharge

# GROSS

- usually exophytic polypoid, sometimes lobulated lesions
- cut surface may be spongy with cystic spaces
- may be multiple polyps (beware recurrent endometrial/cervical polyps)
- tumour may protrude through external os
- occasional cases arise in myometrium, ? from adenomyosis

# CLASSICAL DIAGNOSTIC FEATURES

- club-like/leaf-like/phylloides-like
- bland epithelium of a variety of Mullerian types on surface and lining dilated or slit-like spaces
- cambium layer (stromal condensation)
- intraglandular stromal projections
- stromal hypercellularity
- stromal atypia and mitotic activity (especially in cambium layer)

# PITFALLS

- may get large areas of bland mitotically inactive fibrous or myxoid stroma
- periglandular cuffing may be focal
- mitotic activity may be focal
- need to sample well

# GLANDULAR ELEMENTS

- may get focal proliferation with areas resembling hyperplasia or even endometrioid adenocarcinoma (histogenesis of small minority of carcinosarcomas)

# MYOMETRIAL INVASION

- found in 15-20% of tumours
- usually superficial
- occasionally deep
- rarely get vascular invasion

# MORE UNCOMMON FEATURES

- heterologous elements (rhabdomyoblasts, cartilage etc)
- smooth muscle differentiation
- sex cord-like elements
- angiosarcoma
- stromal decidualisation

# SARCOMATOUS OVERGROWTH

- approximately 10% of cases
- WHO definition-pure sarcomatous component occupies 25% or more of the total tumour volume
- more likely to get deep myometrial and vascular invasion

# IMMUNOHISTOCHEMISTRY

- usual- ER, PR, CD10, WT1 positive, low MIB1 proliferation index, p53 negative
- sarcomatous overgrowth- ER, PR, CD10 negative or decreased, high MIB1 proliferation index, p53 overexpression
- sarcomatous overgrowth- often DNA aneuploidy

# STROMAL COMPONENT

- usual adenosarcoma- stroma is low grade and non-descript fibrous or endometrial stroma-like
- with sarcomatous overgrowth- stroma is usually high grade (like undifferentiated sarcoma)

# DIFFERENTIAL DIAGNOSIS

- **ADENOFIBROMA**
- endometrial or cervical polyp
- atypical polypoid adenomyoma
- carcinosarcoma
- ESS with glands
- pure sarcoma with entrapped glands
- embryonal rhabdomyosarcoma

# DOES ADENOFIBROMA EXIST?

- much more uncommon than adenosarcoma
- ? should ever diagnose on biopsy or curette
- ? should regard all as low grade or well differentiated adenosarcomas

# WHO DEFINITION OF ADENOSARCOMA

- mesenchymal mitotic figures greater than one per 10 HPF (some use  $>2$  per 10 HPF) are required
- in practice, make diagnosis of adenosarcoma if characteristic morphological features are present without associated mitotic activity

# ARGUMENT FOR NOT DIAGNOSING ADENOFIBROMA ON BIOPSY

- sampling issues
- need to see all of lesion
- areas resembling adenofibroma are present in many adenosarcomas

# ARGUMENT FOR NOT DIAGNOSING ADENOFIBROMA ON HYSTERECTOMY

- adenofibromas may recur
- occasional cases diagnosed as adenofibroma on basis of mitotic count have metastasised
- ? call all adenosarcoma but stress that at lower end of spectrum and outcome is likely to be good

# ENDOMETRIAL STROMAL SARCOMA WITH GLANDULAR DIFFERENTIATION

- may occur in uterine and extrauterine ESS
- when projects from a surface, may closely mimic adenosarcoma
- some morphologic overlap between ESS with glands and adenosarcoma (areas may be virtually indistinguishable)

# CERVICAL EMBRYONAL RHABDOMYOSARCOMA

- ? adenosarcoma
- ? entrapped glands

# MANAGEMENT OF ADENOSARCOMA

- hysterectomy (? conserve ovaries in young)
- little role for radiotherapy or chemotherapy unless adverse features present
- ? role of adjuvant therapy with deep myometrial invasion or sarcomatous overgrowth
- ? if lesion removed by polypectomy, patient wishes to preserve her fertility and has adenofibroma/adenosarcoma at low end of spectrum

# FEATURES PREDICTIVE OF ADVERSE BEHAVIOUR

- MYOMETRIAL INVASION (ESPECIALLY DEEP)
- extrauterine spread (very rare)
- vascular invasion (rare)
- SARCOMATOUS OVERGROWTH
- rhabdomyosarcomatous differentiation in one study

# BEHAVIOUR

- potential for local recurrence in pelvis or vagina (approximately 25% of cases)
- most recurrences occur with myometrial invasion or sarcomatous overgrowth
- recurrence may be late
- recurrence may be pure sarcoma or adenosarcoma
- metastasis may occur (approx 5% of cases) most commonly in association with sarcomatous overgrowth (metastatic disease is usually sarcoma)
- occasional tumours without sarcomatous overgrowth or myometrial invasion recur or metastasise