The rare of the rare…

- Uncommon tumors arising from mesenchymal elements
- Most common: CS → LMS → ESS → AS
- Vs. Endometrial cancer → look, spread, and are Rx’d differently
- Heterogeneous group → separate out groups clinically

Leiomyosarcoma

- Median age of diagnosis- 55 years
- Vaginal bleeding most common symptom (56%), followed by a palpable pelvic mass (54%), and pelvic pain (22%)
- Difficult to establish a pre-operative diagnosis
  → pt/surgeon "surprised", limited surgery more common
- Considerable complexity of histologic criteria necessary for the diagnosis of LMS, with a variety of smooth ms tumors from which LMS must be distinguished

Clinico-path characteristics

- Clinico-path study of uterine sarcomas → TAH/BSO/ LND
- 530 pts enrolled → 59 uterine LMS
- Extra-uterine spread was infrequent
  → LN (+) 4%, Adnexa 3%, Cytology 5%
- Pathologic characteristics
  → 50% tumors 6-10 cm, LVSI (+) 34%
  → Mitoses/ 10 HPF: 15% (10-15), 20%(16-20), 60% (>20)

Behavior

- Aggressive tumor- 5yr survival: 25-75%, risk recurrence 45-73%
- GOG series (N=59)
  → 3 yr PFS 31%
  → 1st site failure: lung 41%, pelvis 14%
  → mitotic rate independent predictor PFS
- Mayo series (N=208)
  → Median DSS ≈5 yrs- survival assoc lower stage, lower grade, < 51yr, tumor < 5 cm
  → ovarian preservation assoc with better survival


Giuntoli. Gynecol Oncol. 2003;89:460-469.
 Treatment

• No demonstrated value of any adjuvant therapy
  – Observation vs pelvic radiation vs chemotherapy
• Doxorubicin
• Docetaxel/Gemcitabine
  – GOG 131G- 1 prior → RR 27%, med OS 6+ mo
  – GOG 87L- no prior → RR 36%, med OS 16+ mo
  – Adjuvant use stage I-IV → stage I-II (N=18), 2 yr PFS 59%

Hensley. Gyn Oncol 2009; in press

 Where we struggle…

• With evolving data that the combination docetaxel/gemcitabine regimen may be (for the first time) an effective strategy:
  – are there characteristics of uterine LMS which speak to aggressiveness and poor prognosis (pathologic prognostic factors)
  – are there any pathologic factors that may be predictive of response to (any) therapies.

Endometrial Stromal Sarcoma

• Symptoms- irregular vaginal bleeding, pelvic pain, palpable mass, asymptomatic uterine enlargement
  – Pre-operative diagnosis challenging
• Soft, fleshy, smooth, polypoid masses
• Local invasiveness, (+) LVSI
  – infiltrate and separate the muscle fibers of the uterus.
• Low grade tumors- disease confined to the uterus with Stage I-II disease ~ 70% of series.
• PR (+) common- progestins as adjuvant or for recurrence
• Observation vs pelvic XRT vs progestins

Adenosarcoma

• Unusual tumor with low malignant potential
• Present with abnormal vaginal bleeding
• On gross evaluation → usually polypoid mass can fill the endometrial cavity.
  – Involvement of the cervix and myometrium less common- Myometrial invasion 15%- deeply invasive 4%
• Benign or atypical neoplastic glands with a sarcomatous stroma
• Recurrence in ~25% (mostly local), in one third appeared 5 years after diagnosis
• Sarcomatous overgrowth assoc with increased risk

Where we struggle…

• **Endometrial Stromal Tumors:** Clinically we often think of these tumors as more indolent with favorable biologic behavior. What pathologic characteristics may describe tumors with poorer prognosis.

• **Adenosarcoma:** As these are such rare tumors, what is the differential diagnosis that should be considered in these tumors, and what are distinctive diagnostic criteria that need to be assessed. What are the relevant prognostic features that should be assessed.

Carcinosarcoma

• Post-menopausal bleeding
• Prolapsing polypoid or intracavitary masses
• Masked by high grade epithelial components
• Extraperitoneal spread frequently → intraperitoneal, distant mets @ presentation
Clinico-path characteristics

• GOG study uterine sarcoma N=301 (62%) pts CS
• Extra-uterine spread common
  – LN (+) 17%, Adnexa 12%, Cytology (+) 21%
• Pathologic Characteristics
  – Homologous/Heterologous (55%/45%)
  – LVSI 41%, DOI Outer ½ 36%,

Behavior

• Aggressive behavior
  – 53% of all pts recurred, 43% stage I recurred
  – Pelvic and distant sites of failure common
  • 17% pelvic failure rate after XRT
• Radiation therapy "standard" for many
• EORTC 55874 Stage I-II- RCT
  observation vs XRT ➔ local recurrences
  24% ➔ 14% with XRT, but no impact on PFS/OS

Treatment

• Limited value of adjuvant therapy disease
  – observation vs pelvic XRT vs chemotherapy
• GOG 150- stage I-IV IFX/CDDP vs WART
  – Rec @ 5 yr 51% chemo vs 58% WART
  – Recurrence risk 21% lower for chemo [RH 0.78],
    death rate 20% lower [RH 0.71]-NS
• GOG 161- adv/rec pts IFX vs IFX/paclitaxel
  – RR 29% vs 45%, Med OS 5.8 mo vs 13.5 mo with paclitaxel
• Future…
  – Combine XRT + chemo
  – IFX/paclitaxel vs paclitaxel/carboplatin

Treatment ➔ Directions

• CS are poorly differentiated endometrial adenocarcinomas (EAC) (! vs ?)
  – Molecular markers support common origin of epithelial/sarcomatous components of CS
  – Disease spread/distribution similar Gr3 or PS EAC
  – Outcomes similar to high-risk EAC
  – Treatment moving to the same as EAC ➔
    paclitaxel/carboplatin

Where we struggle…

• What pathologic evidence exists to support or refute that uterine carcinosarcomas are really a manifestation of high grade endometrial cancers.
• There is much debate currently ongoing in developing clinical trials to study uterine carcinosarcomas- should we include them with high grade endometrial cancers or should we treat them as a different entity

Conclusions

• Rare tumors, limited (strong) data ➔ more religion than science
• Pathologists play key role in identifying the “needles in the haystack”

All great truths begin as blasphemies

George Bernard Shaw
SMOOTH MUSCLE TUMORS OF THE UTERUS
PATHOLOGY

Jaime Prat, M.D.

The diagnosis of uterine leiomyosarcoma is usually straightforward since most clinically malignant smooth muscle tumors of the uterus show the microscopic constellation of hypercellularity, severe nuclear atypia, and high mitotic rate generally exceeding 15 mitotic figures per 10 high-power-fields (MF/10 HPF).1-3 Frequently, one or more supportive clinicopathologic features such as peri- or postmenopausal age, extrauterine extension, large size (over 10 cm), infiltrating border, necrosis, and atypical mitotic figures are also present.3 In contrast, the minimal pathologic criteria for a diagnosis of leiomyosarcoma are more problematic and, in such cases, the differential diagnosis has to be made, not only with a variety of benign smooth muscle tumors that exhibit atypical histologic features and unusual growth patterns, but also with smooth muscle tumors of uncertain malignant potential (STUMP).

The specific subtypes of leiomyoma that mimic malignancy are:

- Mitotically active leiomyoma
- Cellular leiomyoma
- Hemorrhagic leiomyoma and hormone-induced changes
- Leiomyoma with bizarre nuclei (atypical leiomyoma)
- Myxoid leiomyoma
- Epithelioid leiomyoma
- Leiomyoma with massive lymphoid infiltration

Mitotically active leiomyoma (MAL)

In premenopausal women, otherwise typical leiomyomas may occasionally show 5 or more MF/10 HPF. These tumors have a benign clinical course (even when treated by myomectomy).4-5 Mitotic rate is usually 5-9 MF/10 HPF, but occasional MAL with 10-20 MF/10 HPF have been reported. The tumors are typically small (<10 cm) and have a benign gross appearance. Tumors exhibiting severe nuclear atypia, abnormal mitoses, or tumor necrosis should not be diagnosed as MALs. Approximately 60% of MALs are submucosal leiomyomas.

Cellular leiomyoma

Leiomyomas that are unusually cellular but otherwise typical have a clinical behavior identical to usual leiomyomas.6,7 Grossly, cellular leiomyomas may resemble typical leiomyomas but often have a fleshier sectioned surface. Microscopically, cellular leiomyomas almost always have < 5MF/10 HPF and are cytologically bland. Cellular leiomyomas may resemble endometrial stromal tumors. Helpful features in the differential diagnosis are:

- Coexistence of the highly cellular areas with a fascicular growth pattern typical of smooth muscle tumors.
- Reticulin fibers that tend to parallel the fascicles of cells in leiomyomas but surround individual tumor cells in endometrial stromal tumors.
- Vessels of large caliber with thick muscular walls; in contrast to the prominent network of small blood vessels typical of endometrial stromal tumors.
• Strong and multifocal or diffuse immunoreactivity for smooth muscle markers such as desmin and h-caldesmon.

In the absence of vascular invasion, the distinction is between two benign lesions; i.e., cellular leiomyoma and endometrial stromal nodule. However, when there is intravascular tumor, the differential is clinically relevant; i.e. intravenous leiomyomatosi versus endometrial stromal sarcoma. In young women wishing to retain their fertility or in older women with high surgical risk, hysteroscopy, imaging studies or repeat sampling should be considered before hysterectomy.

**Hemorrhagic leiomyoma and hormone-induced changes**

Various morphologic changes may be seen in leiomyomas from pregnant women and those on progestin therapy. These include hemorrhage, edema, myxoid change, focal hypercellularity, nuclear pleomorphism, and increased mitotic activity. Patients may present with acute abdominal signs secondary to rupture of the tumor into the peritoneal cavity. Microscopic examination reveals densely cellular proliferations of smooth muscle cells surrounding geographic zones of recent hemorrhage. Although the tumor cells lack malignant nuclear features, as many as 8 MF/10HPF have been encountered in some cases.

Leiomyomas treated with gonadotropin-releasing hormone agonists (GnRHa) to reduce their size prior to their removal, may exhibit the features of apoplectic leiomyomas, and vascular changes (i.e., myxoid change, fibrinoid change, mural thickening, luminal narrowing, and thrombosis). Leiomyomas removed several weeks after withdrawal of GnRHa treatment may have increased mitotic activity.

**Leiomyoma with bizarre nuclei (atypical leiomyoma)**

As an isolated finding, nuclear atypia, even when severe, is an insufficient criterion for the diagnosis of leiomyosarcoma. Occasionally, leiomyomas may contain cells with bizarrely shaped, multilobated or multinucleated, hyperchromatic nuclei. The atypical cells may be distributed throughout the leiomyoma or, more frequently, in discrete perivascular foci. These tumors are variously referred to as "atypical", "symplastic", or "bizarre" leiomyomas. Grossly, these tumors may resemble conventional leiomyomas or may show yellow to tan areas, hemorrhage, or myxoid change.

Microscopically, the defining feature is the presence of bizarre pleomorphic cells with abundant eosinophilic cytoplasm, prominent nuclear pseudoinclusions, and atypical nuclei distributed throughout the tumor or in discrete foci. Typically, the areas uninvolved by the bizarre cells show bland cytologic features. Although most of the atypical cells are multinucleated, mononucleated are also seen. The nuclei are often pyknotic with dense smudged chromatin. A worrisome feature in some tumors is a high mitotic count, up to 7MF/10 HPF by the highest count method. By the average method, however, it ranges from 0 to 2.8 MF/10 HPF (mean 0.8). Confusion with leiomyosarcoma can be enhanced when degenerating or karyorrhectic nuclei are mistaken for atypical mitotic figures.

Leiomyomas with bizarre nuclei are distinguished from leiomyosarcomas by an absence of tumor cell necrosis and mitotic counts of < 10MF/10 HPFs. A mitotic index higher than 10 MF/10 HPF in an atypical smooth muscle tumor is diagnostic of malignancy. Combination of aneuploidy and high MIB-1 activity is rare in bizarre leiomyomas and, in such cases, the diagnosis should be made with caution. Several studies have shown that leiomyomas with bizarre nuclei have a benign clinical course. However, otherwise typical leiomyosarcomas may contain areas indistinguishable from atypical
leiomyomas. In such cases, the finding of atypical mitotic figures and tumor cell necrosis helps in establishing the correct diagnosis.

Myxoid leiomyomas

Myxoid leiomyomas may occur during pregnancy. Grossly, they resemble extrauterine myxomas. Microscopically, they show well-defined borders and contain abundant, acellular, pale-staining material rich in acid mucins which stain with alcian blue or colloidal iron. The neoplastic cells may be elongated or stellate in shape and are widely separated by the extracellular material. Cytologic features are bland and mitotic figures are rare. In curettage specimens, distinction between myxoid leiomyoma and myxoid leiomyosarcoma may be difficult. Non-myxoid portions of the leiomyoma may be erroneously interpreted as evidence of myometrial invasion. In a recent study, a mitotic index of <2 MFs /10 HPFs in the absence of tumor cell necrosis or severe cytologic atypia favored the diagnosis of myxoid leiomyoma. However, large myxoid smooth muscle tumors and those with an infiltrating margin, moderate to severe nuclear atypia, with or without necrosis and any mitotic index, should be regarded myxoid leiomyosarcomas.

Epithelioid leiomyomas

Epithelioid leiomyomas are composed of polygonal cells containing abundant eosinophilic cytoplasm. These tumors are also known as clear cell leiomyomas or leiomyoblastomas. Grossly, they may resemble typical leiomyomas or appear fleshy due to their high cellularity. The average diameter is 6-7 cm. Microscopically, epithelioid leiomyomas often exhibit a diffuse growth pattern, but nests, cords, or pseudoglandular spaces are usually found. The cell cytoplasm is characteristically eosinophilic and granular, but it may be clear (clear cell leiomyoma). The round or angular nuclei are typically central but may be eccentric, occasionally resulting in a signet-ring appearance. Immunohistochemically, these tumors are more frequently positive for cytokeratins and less often positive for smooth muscle markers than nonepithelioid smooth muscle tumors. Because of the rarity of epithelioid smooth muscle tumors, criteria predictive of their malignant behavior are less well established than that for spindle-cell smooth muscle tumors. In an old study of 26 cases, small size, expansile margin, presence of clear cytoplasm, extensive hyalinization, and lack of extensive necrosis are parameters associated with a favorable prognosis; whereas larger tumors (>6 cm) that exhibit 5 or more MFs/10 HPFs should be designated as epithelioid leiomyosarcomas. In a more recent study, the was not a single histologic feature predictive of outcome. Clinically malignant tumors showed grade 3 nuclei, mitotic activity >3/10 HPFs, and tumor cell necrosis. An unpublished study of 32 epithelioid smooth muscle tumors, found that, in the absence of tumor cell necrosis, either moderate to severe nuclear atypia or a mitotic index of 5 or more MFs/10 HPFs warrants a diagnosis of malignancy. Tumors with moderate to severe atypia, without necrosis, and MI < 5/10 HPF should be classified as STUMP.

The differential diagnosis of epithelioid smooth muscle tumors includes primary endometrial or metastatic carcinoma (especially those composed of eosinophilic or clear cells), placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT), and low-grade endometrial stromal sarcoma. Desmin immunoreactivity, absence of the characteristic features of PSTT and ETT, and lack of the vascular-space invasion typically seen in low-grade endometrial stromal sarcoma facilitate the correct diagnosis.

Recently, a low-grade mesenchymal tumor of the soft tissues and uterus thought to derive from perivascular epithelioid cells has been described as PEComa. The tumor cells are arranged in sheets or solid nests, contain oval to round nuclei, exhibit abundant clear or eosinophilic cytoplasm,
and often express smooth muscle markers. PEComas typically immunoreact for HMB-45 and other melanocytic markers such as Melan A.\textsuperscript{15,16} Some tumors may be associated with lymphangioleiomyomatosis and the tuberous sclerosis syndrome. As experience with these tumors is very limited, their long-term prognosis is unknown. Some cases have behaved aggressively.\textsuperscript{15,16}

Rarely, leiomyomas may contain a massive lymphoid infiltrate that may be confused with lymphoma or inflammatory pseudotumor, which rarely may involve the uterus.

Smooth muscle tumors with unusual growth patterns

The designation leiomyoma with vascular invasion refers to an otherwise typical leiomyoma with microscopic intravascular growth confined to the tumor.\textsuperscript{1} Although most of these tumors are clinically benign, several cases have been associated with benign smooth muscle nodules in the lungs (benign metastasizing leiomyoma, see below) while other cases may represent an early stage of intravenous leiomyomatosis.

Leiomyoma with vascular invasion should be distinguished from intravenous leiomyomatosis, a very rare tumor characterized by nodular masses of benign-appearing smooth muscle cells growing within veins beyond the confines or in the absence of a leiomyoma.\textsuperscript{17-19} Extravertebral extension into the pelvic veins and vena cava has been reported in 80\% and over 10\% of patients, respectively. In some cases, the tumor has reached the right side of the heart, sometimes with fatal consequences.\textsuperscript{18,20} The median age of patients with intravenous leiomyomatosis is 45 years.

Grossly, the myometrium contains multiple nodules with wormlike extensions into the uterine veins in the broad ligament. On section, the masses vary from soft to rubbery and firm, and appear pink-white or gray. On histologic examination, the intravascular growth usually resembles a typical leiomyoma, but occasionally it is reminiscent of one or another variant of leiomyoma.\textsuperscript{21} The intravenous tumor has often a clefted or lobulated contour, and its appearance may be altered by extensive hydropic change or hyalinization, and numerous thick-walled vessels. Arteries are not involved. Mitotic figures are usually rare, but cellular intravenous leiomyomatosis may contain up to 4 MFs/10 HPFs. In contrast to low-grade endometrial stromal sarcoma, cellular intravenous leiomyomatosis typically shows thick-walled blood vessels in its intravascular extension. Intravenous leiomyomatosis is a hormonally dependent tumor.\textsuperscript{17,18} GnRH-agonists may be useful in controlling unresectable tumor.

Diffuse leiomyomatosis is a rare lesion characterized by symmetrical uterine enlargement due to innumerable small smooth muscle nodules.\textsuperscript{22} The uterus may be weighing up to 1000 g. The nodules range from microscopic to 3 cm in size. Microscopically, they are composed of uniform, cytologically bland, mitotically-inactive, spindled smooth muscle cells and are less circumscribed than typical leiomyomas. Differential diagnosis includes rare cases of uterine involvement by lymphangioleiomyomatosis, usually in patients with tuberous sclerosis (autosomal dominant disorder; facial angiofibromas, retinal hamartomas, and renal angiomyolipomas). The smooth muscle cells of lymphangiomyomatosis are immunoreactive for HMB-45.

Benign metastasizing leiomyoma is a rare disorder characterized by ‘metastatic’ nodules of benign-appearing smooth muscle in the lung, lymph nodes, or abdomen of women, most of whom have a history of uterine leiomyomas removed previously.\textsuperscript{23,24} Typically, the primary tumor has been resected many years prior to the development of extraterine disease. Often, the primary tumor has been inadequately studied and mitotic counts are not recorded. Some cases may represent deportation metastases from intravenous leiomyomatosis. Others may result from smooth muscle proliferation involving the uterus and extrauterine sites. A recent cytogenetic study has favored the monoclonal origin of both uterine and pulmonary tumors and interpreted the pulmonary tumors as metastatic.
Disseminated peritoneal leiomyomatosis (DPL) is a rare condition characterized by widespread nodules of benign smooth muscle on the peritoneal surfaces in women of reproductive age. Most patients have uterine leiomyomas at the time of diagnosis. DPL is frequently associated with pregnancy, functioning granulosa cell tumors, or oral contraceptives. The most common presentation is as an incidental finding at the time of cesarean section. The intraoperative appearance of DPL is so alarming that frozen section examination is often requested to rule out peritoneal carcinomatosis. The nodules are usually small (<1 cm in diameter), firm, grayish-white, and cover the peritoneal surface of the uterus, adnexa, intestines, and omentum; this differs from metastatic leiomyosarcoma, in which the nodules tend to be fewer, larger, and invasive into adjacent tissues. Microscopically, the nodules of DPL consist of smooth muscle cells, fibroblasts, myofibroblasts, and, in pregnancy or the postpartum, decidual cells. Nuclear pleomorphism and hypercellularity are absent. Mitotic figures are inconspicuous. Lymph node involvement may occur. DPL expresses desmin, smooth muscle actin, CD10, and ER and PR. The etiology of DPL is unknown. A metaplastic transformation of the subperitoneal mesenchyme has been proposed. DPL may regress after therapy with GnRH agonist. Five cases of malignant DPL have been reported and recently reviewed.

Leiomyosarcomas

After excluding carcinosarcomas, which are now classified as a dedifferentiated or metaplastic form of endometrial carcinoma, leiomyosarcomas are thought to represent the most common form of uterine sarcoma. However, they only account for 1-2% of uterine malignancies. Most occur in women over 40 years of age who frequently present abnormal vaginal bleeding, pain or both. Occasionally, the presenting manifestations are related to tumor rupture (hemoperitoneum), extrauterine extension (one-third to one-half of cases), or metastases. Only very rarely, a leiomyosarcoma originates from a leiomyoma.

Macroscopic features

Typically large solitary masses with a mean diameter of 10 cm. Approximately 25% of the tumors are < 5 cm in size. About two-thirds of leiomyosarcomas are intramural, 1/5 submucosal, and 1/10 subserosal; 5% arise in the cervix. They are almost always less circumscribed than leiomyomas. The cut surface is typically bulging, fleshy, focally necrotic, and hemorrhagic. When a myometrial tumor shows an unusual gross appearance, thorough sampling is recommended (at least one section per cm in diameter). Leiomyosarcomas are either a single mass or -when associated with leiomyomas- the largest mass.

Microscopic features

On microscopic examination, most uterine leiomyosarcomas are obviously malignant and, besides destructive myometrial invasion, show:

- At least, moderate hypercellularity.
- Moderate to marked nuclear atypia, usually diffuse.
- High mitotic rate (10 or more MFs /10 HPFs; over 90% have > 15 MFs/10 HPFs).
- Tumor necrosis (geographic necrosis), characterized by an abrupt transition from the viable cells to the necrotic cells without an interposed zone of granulation tissue or fibrous tissue. Preserved nuclei with marked pleomorphism and hyperchromasia can still be seen within the necrotic areas and often there is a perivascular growth of viable tumor cells. Tumor necrosis is highly characteristic of leiomyosarcomas.
Tumor necrosis should be distinguished from infarct-type necrosis (which may be seen in benign or malignant smooth muscle tumors) and is characterized by a transition zone composed of granulation or fibrous (hyalinized) tissue depending upon the age of the infarct. The necrotic tissue has a mummified and homogeneous appearance, areas of hemorrhage are common, and no perivascular growth of tumor cells is seen. According to Bell et al., the presence of 2 of the 3 criteria (nuclear atypia, high mitotic rate, and tumor cell necrosis) warrants a diagnosis of leiomyosarcoma. In some cases, distinguishing between tumor necrosis and infarct-type necrosis may be difficult.

Leiomyosarcomas are aggressive tumors. In a large Gynecology Oncology Group (GOG) study, the recurrent rate was 71%. First recurrences were in the lungs in 40% of patients, and in the pelvis in only 13%. Survival rate ranged from 15% to 25%, with a median survival of only 10 months in one study. There has been no consistency among various studies regarding correlation between survival and patient age, clinical stage, tumor size, type of border (pushing versus infiltrative), presence or absence of necrosis, mitotic rate, degree of nuclear pleomorphism, and vascular invasion. One study, however, found tumor size to be a major prognostic parameter: five of 8 patients with tumors < 5 cm in diameter survived, whereas all patients with tumors > 5 cm in diameter died of tumor. In this study of 208 uterine leiomyosarcomas, the only parameters predictive of prognosis were tumor grade and stage. Tumor grade, however, has not been consistently identified as a significant prognostic parameter. Possibly, many of the so-called “low-grade” leiomyosarcomas may in fact represent histologic variants of leiomyomas frequently misdiagnosed as sarcomas (such as cellular, mitotically active, epithelioid, myxoid, and atypical leiomyomas).

Rare malignant smooth muscle tumors lacking the high mitotic activity of typical leiomyosarcomas include epithelioid and myxoid leiomyosarcomas.

**Epithelioid leiomyosarcomas** are composed predominantly or entirely of round or polygonal cells exhibiting eosinophilic or clear cytoplasm. Tumor cells grow diffusely in nests, cords, or forming a plexiform pattern. Although nuclear pleomorphism is usually mild, some tumors show moderate to marked nuclear atypia. Mitotic rate is generally <3 MFs/10 HPFs. Most tumors infiltrate the adjacent myometrium but vascular invasion is rare. Necrosis may be absent. Three of 26 tumors in one series recurred or metastasized. The malignant tumors exhibited one or more of the following features: eosinophilic cells, infiltrating margin, necrosis, diameter greater than 6 cm, and absence of hyaline stroma.

**Myxoid leiomyosarcomas** are grossly gelatinous (>50%) and microscopically show a sparsely cellular, myxoid appearance. In contrast to conventional leiomyosarcomas, most tumors are hypocellular. Myxoid leiomyosarcomas are almost always clinically malignant despite low mitotic rates (0-2 MFs/10 HPFs) and bland nuclear features; in the absence of severe cytologic atypia and tumor cell necrosis, they are diagnosed as sarcomas based on their infiltrative borders. They show abundant basophilic or eosinophilic myxoid matrix that reacts strongly with alcian blue and colloidal iron. Smooth muscle markers are detected immunohistochemically in <25% of tumor cells.

Recently, several immunohistochemical and molecular genetic studies on uterine leiomyosarcomas have been reported. Although leiomyosarcomas usually express smooth muscle markers such as desmin, h-caldesmon, smooth muscle actin, and HDCA8. Epithelioid and myxoid leiomyosarcomas may show lesser degrees of immunoreaction for these markers. Conventional leiomyosarcomas express ER, PR, and AR in 30-40% of cases. Also, immunoreaction for CD117 (but no c-kit mutations) has been found. Several studies have shown that uterine leiomyosarcomas have a significantly higher Ki67 index than benign smooth muscle tumors. Mutation and overexpression of p53 have been described in uterine leiomyosarcomas. It has been reported that 32% and 83% of leiomyosarcomas showed
p53 immunoreaction in >50% and >25% of the tumor cells, respectively. In contrast, only 4% of the atypical leiomyomas exhibited a positive p53 immunoreaction.

Overexpression of p16 has recently been described in uterine leiomyosarcomas and found to be higher than in leiomyomas.35-37 In the former tumors, its reported frequency ranged from 57% to 100% and immunoreaction was found in from >25% to >50% of tumor cells. Contrariwise, 13% or less of uterine leiomyomas showed p16 immunoreaction. In one study, however, up to 60% of atypical (bizarre) leiomyomas showed immunostaining for p16.37 Another study revealed a correlation between p16 overexpression and poor outcome.35

Smooth muscle tumors of uncertain malignant potential (STUMP)

Combining the results of 8 series in the literature, Zaloudek and Norris,1 found that 75% of cellular smooth muscle tumors with mitotic rates of 5 or more MFs/10HPFs were clinically malignant (i.e. leiomyosarcoma), whereas those with 4 or fewer MFs/10HPFs were almost invariably benign; all of the clinically malignant tumors were cytologically atypical. Therefore, the criteria proposed by these authors for leiomyosarcoma were the simultaneous presence of 5 or more MFs/10HPFs and cytologic atypia.

Uterine smooth muscle tumors that are unclassifiable by current criteria as unequivocally benign or malignant have been referred to as smooth muscle tumors of uncertain malignant potential (STUMP) although as yet there is no uniform definition of these tumors. Criteria used by Bell et al.25 include moderate to severe cytologic atypia and <10 MFs/10 HPFs in absence of tumor necrosis. In contrast, O'Connor and Norris4 render a diagnosis of STUMP when there are 5-9 MFs/10 HPFs and mild (grade 1/3) nuclear atypia. STUMPs were subdivided in the study by Bell et al.25 into three groups:

a) Atypical leiomyoma with low risk of recurrence, showing diffuse moderate to severe atypia, <10 MFs/ 10 HPFs, and no tumor cell necrosis. Only one of 46 such tumors was clinically malignant.

b) Atypical leiomyoma but limited experience, was characterized by focal moderate to severe atypia, <20 MFs/ 10 HPFs, and no tumor cell necrosis. There were only five cases in this group and all were clinically benign. Three of the five tumors had <5 MFs/ 10 HPFs and would be considered leiomyomas with bizarre nuclei by most investigators. The other two tumors had 10-19 MFs/10 HPFs.

c) Smooth muscle tumors of low malignant potential, had tumor cell necrosis, <10 MFs/ 10 HPFs, and absent to mild atypia. One of four tumors in this group was clinically malignant, again underscoring the importance of tumor cell necrosis.

Currently, it is believed that leiomyosarcomas are associated with poor prognosis even when confined to the uterus (stage I). Conversely, most tumors classified as STUMP have been associated with favorable prognosis and, in these cases, only follow-up of the patient is recommended.
REFERENCES


Smooth Muscle Tumors of the Uterus

Pathology

Jaime Prat, M.D.
Hospital de la Santa Creu i Sant Pau
Autonomous University of Barcelona, Spain

Smooth Muscle Tumors of the Uterus

(Outline)

• Typical leiomyosarcoma
• Rare variants (Epithelioid & Myxoid)
• Leiomyoma variants (WHO 2003)
• Prognostic factors (lack of...)
• Staging
• Minimal pathologic criteria
• Uncertain malignant potential

Uterine Sarcomas

(3% of Uterine Cancers)

• Leiomyosarcomas 30%
• Mg Mixed Mesodermal Tumors 50%
  (Carcinosarcomas)
• Endometrial Stromal Sarcomas 15%
• Undifferentiated Sarcomas 5%

Leiomyosarcoma

• Dx is usually straightforward
• Over 90% of cases:
  • Hypercellularity
  • Marked nuclear atypia
  • High mitotic rate (15 MF/10 HPF)

Smooth Muscle Tumors of the Uterus

Leiomyosarcoma

(Additional relevant findings)

• Peri- or postmenopausal age
• Extrauterine extension
• Diameter over 10 cm
• Infiltrating border
• Coagulative necrosis
• Atypical mitoses

Perrone T, Dehner LP.
Leiomyosarcoma

(Rare variants)

- Epithelioid LMS
- Myxoid LMS

Epithelioid Leiomyosarcoma

- Diameter > 6 cm
- Infiltrative margin
- 3-5 mitoses/10 HPF
- Necrosis +/-

Myxoid Leiomyosarcoma

- Gelatinous/myxoid (>50%)
- Infiltrative borders
- Bland nuclear features
- 0-2 mitoses/10 HPF (40%)
- Smooth muscle markers (<25% of tumor cells)
- CD10 + / ALK-1 -
- Poor prognosis

Leiomyosarcomas

- Most uterine sarcomas are leiomyosarcomas
- The vast majority of leiomyosarcomas are high-grade sarcomas associated with poor prognosis
- 259 patients from Norway: 51% 5 yr survival (IGCS 2008)
- Application of 2003 WHO criteria
- Possibly, many of the so-called “low-grade” leiomyosarcomas may in fact represent histologic variants of leiomyomas frequently misdiagnosed as sarcomas

Leiomyoma-variants

- Mitotically active leiomyoma (MAL)
- Cellular leiomyoma
- Epithelioid leiomyoma
- Leiomyoma with bizarre nuclei
- Leiomyoma with vascular invasion
- Intravenous leiomyomatosis
- Benign metastasizing leiomyoma
- Diffuse leiomyomatosis

Mitotically Active Leiomyoma

(Up to 15 Mit/10HPF)

- Small (< 10 cm)
- Grossly benign
- Submucosal
- No nuclear atypia
- Young women
- Secretory phase
- Pregnancy/Progestins
**Cellular Leiomyoma**

- Fascicular growth pattern
- Thick-walled vessels
- Positive desmin/h-caldesmon
- Misdiagnosed as stromal tumor

Oliva E et al.  

---

**Epithelioid Leiomyoma**

- Nests, cords, pseudoglands
- Eosinophilic or clear cells
- No necrosis/No atypia
- Hyalinization
- < 5 mitoses/10 HPF
- Positive CK
- Diff Dx: Carcinoma

Prayson RA et al.  

---

**Bizarre Leiomyoma**

(24 cases with Follow-up)

- Age: 25 - 51 (av 40) yr
- Size: 1 - 14 (av 4.2) cm
  - 8% >10 cm
- Color: yellow-tan (33%)
- Border: sharp (50%)
- Cell: 1+ (21%), 2+ (58%), 3+ (21%)
- Giant cells: focal (12.5%)
  - multif (37.5%)
  - diff (50%)
- Tumor necrosis: 0/24

Downes & Hart  

---

**Bizarre Leiomyoma**

(24 cases with Follow-up)

- Mitosis: Average 0-2.8/10 HPF (m 0.8)
  - Highest 0-7/10 HPF (m 1.6)
- Hysterectomy: 20/24
- Myomectomy: 6/24 (+2 Hysterectomy)
- Follow-up: 1.0-18.9 (m 11.2) yr
- All alive and well

Downes & Hart  

---

**Bizarre Leiomyoma versus Leiomyosarcoma**

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>LMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic count</td>
<td>&lt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Tumor cell necrosis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>DNA ploidy</td>
<td>Diploid</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>MIB-1</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>p53</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Downes KA and Hart WR, 1999

---

**A note of caution:**

Leiomyosarcomas may show superimposed “bizarre” change!
Intravenous Leiomyomatosis

- Extrauterine extension 80%
- Leiomyoma or variants
- Thick-walled vessels
- Up to 4 mitoses/10 HPF

Leiomyosarcomas are high-grade sarcomas associated with poor prognosis even if at Stage I

Uterine Leiomyosarcomas (5 yr Surv)

Stage I 40-70%
Overall 15-25%

Staging of Uterine Leiomyosarcomas

<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>&lt; 5 cm</td>
</tr>
<tr>
<td>IB</td>
<td>&gt; 5 cm</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends to the pelvis</td>
</tr>
<tr>
<td>IIIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumor extends to extrauterine pelvic tissue</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>&gt; one 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 and/or distant metastasis</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Leiomyosarcomas (Inconsistent Prognostics Factors)

- Age
- Stage
- Size
- Border (pushing vs infiltrative)
- Necrosis
- Mitosis
- Nuclear atypia
- Vascular invasion

Cellular & Atypical Smooth Muscle Tumors of the Uterus

5+ Mit/10HPF Malignant (75%)
4- Mit/10HPF Benign

Zaloudek & Norris, 1981
## Uterine Smooth Muscle Tumors

<table>
<thead>
<tr>
<th>Atypia</th>
<th>Tumor Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>+</td>
<td><em>+</em></td>
</tr>
<tr>
<td>&gt;10</td>
<td>&gt;10 &lt;10 5-20</td>
</tr>
</tbody>
</table>

- LMS: Low Risk
- LM: Malignant

Bell SW et al., 1994

* diffuse or focal

### Smooth Muscle Tumors of Uncertain Malignant Potential

**"STUMPS"**

- Tumor cell necrosis in a typical leiomyoma
- Necrosis of uncertain type with 10 or more MFs/10 HPFs, or marked diffuse atypia
- Marked diffuse atypia with borderline mitotic counts
- Marked focal atypia and 10 or more MFs/10 HPFs

### Leiomyosarcomas

(Immunohistochemistry)

- Proliferation markers (Ki-67, p53, p16, Twist) are usually overexpressed
- A subset of LMS lacking proliferation markers and expressing bcl-2 may be associated with good prognosis

D'Angelo E, et al., 2009

### Smooth Muscle Tumors of the Uterus (Summary)

- Leiomyosarcomas are high-grade tumors
- Leiomyoma variants (overdiagnosis)
- Leiomyosarcomas may show "bizarre" change
- Minimal diagnostic criteria: mitoses are necessary but insufficient (size, atypia, necrosis)
- Epithelioid and Myxoid tumors (watch out!)
- Uncertain malignant potential (follow-up)
Smooth Muscle Tumors - Molecular Biology

C.B. Gilks MD FRCPC
Vancouver General Hospital and the University of British Columbia

Uterine Leiomyoma
The majority of uterine leiomyomas (ULM) occur sporadically, however there appears to be a component of genetic susceptibility to the development of ULM in some cases, as familial aggregation has been noted [1]. The syndrome of multiple cutaneous and uterine leiomyomatosis/hereditary leiomyomatosis and renal cell carcinoma is associated with the development of ULM [2-4]. Patients with this syndrome have germline inactivating mutations in a single copy of the fumarate hydratase (FH) gene and are susceptible to the development of multiple cutaneous leiomyomas (at young age) and symptomatic ULM [5], in addition to renal cell carcinomas [6]. Loss of FH through a somatic mutation has also been reported in occasional non-syndromic (sporadic) cases of ULM [7].

By cytogenetic and conventional FISH analysis, most ULM display normal karyotypes [8]. Approximately 40% of ULM have non-random cytogenetic changes but in contrast to LMS, these alterations typically involve only a small number of chromosomal regions and are less complex in nature [8,9]. The most frequent cytogenetic alterations are t(12;14), deletion of 7q and chromosome 12 trisomy, detected in approximately 20%, 17% and 10% of cases respectively [4,8,10]. Other less frequent cytogenetic alterations include 6p and 10q rearrangement and deletion of 3q. Though not well substantiated, there appears to be a tendency for the karyotypically abnormal tumors to be more cellular and/or mitotically active histologically, and to be more frequently intramural or subserosal in location [11,12]. t(12;14) translocation is specific for leiomyoma and involves HMGA2, a putative DNA binding transcriptional regulator. This gene is frequently rearranged in other mesenchymal tumors such as aggressive angiomyxomas and lipomas [13-15]. Other types of structural rearrangements involving HMGA2 have also been described for ULM [8]. Further analysis has revealed that the full coding sequence of HMGA2 is typically retained regardless of the type of rearrangement and it appears that these rearrangements result in increased levels of functional active HMGA2. Furthermore, increased expression of HMGA2 at both mRNA and protein levels is commonly observed in ULM, with the highest levels in tumors with t(12;14)[16]. HMGA2 therefore appears to play a central role in the development and progression of at least a subset of ULM. Diagnostically, DNA copy number gain and increased expression of HMGA2 gene are also observed in uterine leiomyosarcomas (LMS) [17,18], and cannot be used reliably to predict benignancy or malignancy in uterine smooth muscle tumors. Even though t(12;14) has not been reported to occur in uterine LMS to date, it lacks sensitivity for detection of ULM.

In keeping with the cytogenetic observations, conventional or array comparative genomic hybridization (CGH) analyses shows no alterations in gene copy number, or only a few foci of genomic gains or losses, in contrast to the multiple complex genomic aberrations observed for uterine LMS [17,19,20]. Overall, no aberrations common to both ULM and uterine LMS were found.
The gene expression profile of ULM has also been examined in detail, particularly in comparison to that of normal myometrium, and many differentially regulated genes implicated in increased cell growth/proliferation and increased extracellular matrix deposition have been identified by these analyses [1,9,21-24]. Genes implicated in growth stimulation include upregulation of IGF2 and PKCB1 and genes implicated in increased ECM deposition include upregulation of TGFB3 and MMP11. ESR1 is also frequently upregulated in ULM and this is in keeping with the consistent immunohistochemical expression of estrogen receptor as well as progesterone receptor in ULM. It is now believed that both estrogen and progesterone stimulation are important in promoting the growth of ULM [25-27]. Another emerging type of high throughput genetic analysis involves profiling of microRNA (miRNA) expression patterns in tumor samples. MiRNAs are 20–25 nucleotide non-coding RNAs that inhibit the translation of targeted mRNAs, and represent an important epigenetic regulatory mechanism. A few studies have examined the miRNA expression profiles of ULM and found dysregulation of several miRNA in comparison to matched myometrium samples. Most notably, downregulation of Let-7 was observed in ULM, particularly in larger size tumors [28,29]. Let-7 is able to suppress HMGA2 expression [30] and the downregulation of Let-7 seen in large ULM may represent another important mechanism underlying increased HMGA2 expression. Several studies have also compared the mRNA and miRNA expression profiles between ULM and LMS. ULM and uterine LMS generally exhibit gene and miRNA expression profiles that are significantly different from each other. The details of these comparisons will be addressed below, in the LMS section.

**Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP)**

Little is known regarding the genetics of STUMP. One study reported similar degrees of allelic loss involving common tumor suppressor genes between STUMP and ULM, both of which were significantly lower than that of LMS [31]. Several studies have characterized STUMPs immunohistochemically in relation to ULM and LMS. The majority of STUMPs demonstrate a Mib-1, p16, ER, PR, p53 immunoprofile that is significantly different from LMS but not from that of ULM [32-37], though the Mib-1 proliferation index is typically slightly greater in STUMP than ULM. However, the great majority of STUMPs studied either lacked clinical follow-up data or showed no evidence of disease recurrence. A recent study found the presence of diffuse p16 positivity in two STUMP cases that later developed metastatic disease. Both cases showed the presence of tumor necrosis but no significant atypia or increased mitotic activity [32]. Clearly, more outcome-associated studies are needed to further examine the utility of these and other molecular markers in predicting the clinical behavior of STUMPs. At present those cases diagnosed as STUMP cannot be distinguished, based on molecular markers, from ULM, and within the groups of STUMPs, there are no well-validated molecular markers of increased risk of recurrence.

**Uterine Leiomyosarcoma**

The vast majority of uterine LMS are sporadic. Patients with germline mutations in FH (described previously) are believed to be at increased risk for developing uterine LMS, as well as ULM [38,39].
Cytogenetically, uterine LMS are karyotypically complex with structural changes involving a large number of chromosomes [9]. The degree and extent of karyotypic complexity is similar to that of soft tissue LMS [9]. Both conventional and array based CGH analysis have identified chromosomal imbalances in nearly all uterine LMS examined [17,19,20,40,41]. The imbalances typically involve several chromosomes with comparable number of gains and losses present. No consistent patterns of gains or losses have been observed, particular between different studies. In comparison to ULM, LMS showed greater number and complexity of chromosomal aberrations overall, such that uterine smooth muscle tumors with complex cytogenetic or CGH abnormalities are very likely malignant, however, no single change is sufficiently sensitive or specific to be diagnostically useful.

Gene expression profiling analysis has identified several differentially expressed genes in uterine LMS when compared to normal myometrium and/or ULM [21,42,43]. In comparison to normal myometrium or to ULM, uterine LMS shows upregulation of several cell proliferation associated genes including TOP2A, PTTG1, CDKIN2A, UBE2C, MCM2 and FOXM1, indicating presence of greater degree of disruption in cell proliferation/cell cycle control in LMS. Other differentially expressed genes include the upregulation of SPP1, NNMT, CHI3L1, GRN, IL17B and downregulation of ADH1A, IGF1 and CALD1. CDKIN2A encodes the protein p16 and in keeping with the gene expression findings, expression of p16 (nuclear and/or cytoplasmic) is greater in LMS versus ULM [32,34,37]. p16 therefore may prove to be a useful adjunct immunomarker in distinction between malignant and benign uterine smooth muscle tumors. While the data is current limited, the miRNA expression profiles of uterine LMS appears to differ from that of normal myometrium and/or ULM [44,45]. More specifically, miR-221 was found to be expressed at higher levels in LMS compared to ULM and benign metastasizing leiomyomas [44]. Thus, the evaluation for miR-221 level or levels of other dysregulated miRNA by RNA in situ hybridization (ISH) method may prove to be useful in identifying LMS in diagnostically challenging cases.

By both gene expression and immunohistochemical analysis, ER expression has been reported to be present in between a quarter to two-third of uterine LMS [46,47]. Some studies have reported a correlation between immunohistochemical ER and/or PR expression and improved clinical outcome in patients with uterine LMS by univariate analysis [46,48]. Other genes of interest that have been examined in uterine LMS include tumor suppressor genes such as p53 and RB1, and oncogenes such as c-KIT. Abnormalities in p53 in the form of missense mutation and/or loss of heterozygosity (LOH) are common in uterine LMS [49,50]. Detection of p53 abnormalities by immunohistochemistry has also been employed to differentiate between benign and malignant uterine smooth muscle tumors. It has limited utility as only a subset (~50%) of uterine LMS shows significant p53 immunoreactivity. Prognostically, p53 over-expression has been reported to be associated with poor outcome [51,52]. LOH of RB1 is also commonly seen in uterine LMS [50]. Regarding c-KIT, while variable proportion of uterine LMS has been reported to demonstrate c-KIT immunopositivity, no mutations in c-KIT have been identified in uterine LMS [53-55].

While a large number of genetic abnormalities have been identified, the oncogenic mechanisms underlying development of uterine LMS remain elusive. Overall, uterine LMS is a genetically
unstable tumor that demonstrates complex structural chromosomal abnormalities and highly disturbed gene regulation, and this likely reflect the end-state of the accumulation of multiple genetic defects in the process of tumor development. Extrapolating from the experiences in soft tissue LMS, it is unlikely that recurrent disease-driven genetic aberrations (i.e. gene mutation or translocation events) will be uncovered. In comparison to other more common uterine malignancies, uterine LMS bear some resemblance to type 2 endometrial carcinomas and high-grade serous carcinomas of ovary/fallopian tube origin, based on their genetic instability, frequent p53 abnormalities, aggressive behavior, and resistance to chemotherapy. As such, therapies that exploit the underlying genetic instability of uterine LMS may prove to be an effective therapeutic strategy.
References


ENDOMETRIAL STROMAL TUMORS

Esther Oliva, M.D.
Pathology Department, Massachusetts General Hospital, Boston, USA

Endometrial stromal tumors (EST) of the uterus are the second most common pure mesenchymal tumor of the uterus even though they account for < 10% of all such tumors. In the latest 2003 WHO classification they are divided into:

a) endometrial stromal nodule (ESN)
b) low-grade endometrial stromal sarcoma (ESS)
c) undifferentiated endometrial/uterine sarcoma (UES)

Endometrial stromal nodule and low-grade ESS fall in the lower end of the spectrum of this group of tumors. Both are typically composed of a diffuse growth of small blue cells with scant cytoplasm and oval to spindle nuclei that resemble the stromal cells of the proliferative-phase endometrium. At the other end of the spectrum is the UES, a very high-grade sarcoma which does not resemble the proliferative-phase endometrium. It is a diagnosis that should only be made after excluding other high-grade tumors with a sarcomatous component.

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Clinical features

ESNs are very rare while low-grade ESSs account for approximately 0.2% of all malignant uterine tumors and 10-15% of uterine malignancies with a mesenchymal component. Both tumors frequently occur in women between 40 and 55 years of age. Some low-grade ESSs have been reported in women with ovarian polycystic disease, estrogen use, or tamoxifen therapy. Patients commonly present with abnormal uterine bleeding, pelvic pain, and dysmenorrhea, but as many as 25% of patients are asymptomatic. Extraterine pelvic extension at the time of presentation is found in up to 1/3 of the patients with low-grade ESS, most commonly involving the ovary. Thus, when evaluating an ovarian tumor with a microscopic appearance consistent with an EST, it is important to exclude a prior history of a uterine EST and to suggest inspection of the uterus, as the latter are far more common.

Gross features

*The main differentiating feature between the two neoplasms is tumor circumscription.*

**ESN:** Well circumscribed, although nonencapsulated neoplasm ranging in size from 0.5 to 22 (mean 7) cm. If centered in the endometrium, it is frequently polypoid; but it is often intramyometrial.
**Low-grade ESS:** Frequent irregular nodular growth involving the endometrium, myometrium, or both. The main mass is frequently associated with varying degrees of permeation of the myometrium, including worm-like plugs of tumor that fill and distend myometrial veins, frequently extending to parametrial veins. On rare occasions, low-grade ESSs may appear deceptively well circumscribed on gross examination. In these cases, extensive sampling of the tumor interface is extremely important.

**ESN and Low-grade ESS:** Uniform soft, tan to yellow cut surface which may be associated with cyst formation as well as hemorrhage and/or necrosis.

**Microscopic features**

*Myometrial and vascular invasion are the two most important features in the distinction between ESN and low-grade ESS.*

**ESN**: The most important single criterion is the finding of a non-infiltrative border of the tumor. Focal irregularities in the form of lobulated or finger-like projections into the adjacent myometrium that do not exceed 3 mm and do not exceed 3 in number may be seen. No vascular invasion should be present.

**Low-grade ESS**: The tumor typically permeates the myometrium as irregular tongues and frequently invades myometrial as well as extrauterine veins and lymphatics.

**ESN and low-grade ESS**: The tumors are typically hypercellular but they may be hypocellular secondary to a fibrous or myxoid background. They are composed of sheets of uniform small blue cells closely resembling the proliferative-phase endometrial stroma. The cells have scant cytoplasm and oval to round nuclei with inconspicuous nucleoli. Mitotic activity is typically <5/10 high power fields. Brisk mitotic activity is still compatible with the diagnosis of low-grade ESS if the architectural and cytologic features of the tumor are reminiscent of endometrial stroma. There is frequent whorling of the neoplastic stromal cells around arterioles (the latter may appear hyalinized), but the characteristic arborizing vasculature is not always striking. Sex cord differentiation, smooth and skeletal muscle differentiation, fibrous or myxoid change, glandular differentiation (as benign or malignant endometrioid-type glands), rhabdoid, epithelioid, or clear phenotype as well as fatty metaplasia and bizarre cells may also be seen. Collagen bands or plaques, diffuse areas of hyalinization, foamy histiocytes, cystic degeneration associated with cholesterol clefts, and necrosis may be present in both tumors and are not useful in the differential diagnosis.

*In the majority of cases it is impossible to differentiate between ESN and low-grade ESS on curettage specimens. Thus distinction can only be confidently established in a hysterectomy specimen.* This is an important issue when the patient is of reproductive age and desires to preserve her uterus. In these circumstances, a combination of diagnostic imaging and hysteroscopy may be used to monitor the growth of the tumor and occasionally local excision has been successful.
**Immunohistochemistry**

ESN and low-grade ESS are typically positive for vimentin, muscle-specific and smooth muscle actin, and frequently keratin. Most ESTs stain for CD10. However, smooth muscle tumors, mixed mullerian tumors (including adenosarcoma and malignant mixed mullerian tumor (MMMT)), and rhabdomyosarcomas may be CD10 positive. Thus, this antibody should not be used in isolation when evaluating the cell of origin in a uterine mesenchymal tumor. Desmin staining in ESTs varies among studies and it should not be used in isolation to differentiate ESTs from smooth muscle tumors. Other muscle markers including h-caldesmon, myosin and HDCA8 are also helpful in this differential diagnosis. Areas of smooth muscle differentiation are positive for all smooth muscle markers as well as for CD10. Areas of sex cord-like differentiation may be positive for inhibin, calretinin, CD99, WT-1 and Melan A. Endometrial stromal tumors frequently contain ER and PR, although its presence is not specific to these tumors and they also frequently express β-catenin.

**Cytogenetics**

Conventional ESTs as well as their variants show as most common translocation t(7;17) with involvement of two zinc finger genes, JAZF1 and JJAZ1.

**Differential diagnosis**

Highly cellular leiomyoma most frequently causes problems in the differential diagnosis with either a pure ESN or low-grade ESS, as they share the following features: dense cellularity, prominent vascularity, and an irregular margin with the surrounding myometrium (in some). However, highly cellular leiomyoma has a fascicular growth at the periphery of the lesion, the tumor cells merge with the surrounding myometrium and the vessels are typically thick and large in contrast to the delicate arteriolar network present in ESTs. A cellular endometrial polyp may enter in the differential diagnosis when fragmented and present in a curettage. The inactive appearance of the stromal cells as well as the finding of large vessels and absence of the small arteriolar network will favor the diagnosis of polyp. A uterine tumor resembling a sex cord-stromal tumor (UTROSCT) may enter in the differential diagnosis of and ESN or low-grade ESS as ESTs may show extensive sex cord-like differentiation. A diagnosis of UTROSCT can only be made when no evident endometrial stromal component is seen. Thus, this is only achieved with the hysterectomy specimen. Low-grade ESS with gland differentiation should be distinguished from low-grade mullerian adenosarcoma and adenomyosis.

**Prognosis and treatment**

Patients with an ESN have an excellent prognosis and the treatment of choice is surgery. Patients with low-grade ESSs have a 5-year survival rate of approximately 60 to 80%. These tumors have a low malignant potential and are characterized by late recurrences even in patients with stage I disease, as one third or more develop recurrences, most commonly in the pelvis (occurring in up to one half of the patients) and abdomen, and
less frequently in lung and vagina. Thus, patients require long follow-up. Standard initial surgical treatment encompasses total abdominal hysterectomy and bilateral salpingo-oophorectomy as these tumors are often hormone sensitive and it has been shown that patients retaining their ovaries have a much higher risk of recurrence (up to 100%). Lymph node dissection does not seem to have a role in the treatment of these tumors. Patients may also receive adjuvant radiation or hormonal treatment with progestational agents or aromatase inhibitors. Clinicopathologic factors reported in the older literature to be of potential prognostic importance included age, race, size, FIGO stage, depth of myometrial invasion, tumor grade, mitotic activity, and DNA ploidy. However, in the largest study of low-grade ESS, mitotic activity and cytologic atypia were not predictive of tumor recurrence in stage I tumors (most common scenario), while size poorly correlated with outcome as tumors <4 cm also recurred. Endometrial stromal tumors with unusual types of differentiation should be reported as ESN or low-grade ESS based on the margins, as this is the only discriminating prognostic factor.

**UNDIFFERENTIATED ENDOMETRIAL/UTERINE SARCOMA**

These are extremely rare tumors and the lack of specific evidence of endometrial stromal cell origin in most cases precludes their placement in the endometrial stromal group of uterine tumors. Grossly, they show a fleshy, gray cut surface with common areas of hemorrhage and necrosis. On microscopic examination, there is destructive myometrial invasion while the intravascular worm-like plugs characteristic of low-grade ESS are typically absent. They have marked cellular pleomorphism and brisk mitotic activity. These tumors should be diagnosed only after extensive sampling has excluded smooth or skeletal muscle differentiation or even small foci of carcinoma, as this finding would result in a diagnosis of MMMT. Occasional tumors have a component of low-grade ESS indicating that the high-grade component is presumably of endometrial stromal derivation. In these cases, the designation of high-grade ESS arising from a low-grade ESS is indicated. A recent study has divided high-grade tumors in two categories based on nuclear uniformity. Undifferentiated tumors with nuclear uniformity shared some immunohistochemical and molecular features with low-grade ESS. Undifferentiated endometrial/uterine sarcomas carry a very poor prognosis and most patients die of disease within two years of the initial diagnosis. CD10 expression is not helpful in this differential as UES as well as leiomyosarcoma, rhabdomyosarcoma and MMMT express this marker. Smooth muscle markers and myogenin or myoD1 may be used to rule out leiomyosarcoma or rhabdomyosarcoma respectively, or to identify a rhabdomyosarcoma component in a MMMT.
REFERENCES


ENDOMETRIAL STROMAL TUMORS

WHO Classification

- Endometrial Stromal Nodule
- Low-Grade Endometrial Stromal Sarcoma
- Undifferentiated Endometrial Sarcoma

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

- Shared clinical features:
  - Frequently diagnosed between 40-55 years
  - 1/3 of patients are postmenopausal
  - Abnormal uterine bleeding or pelvic/abdominal pain common presentations
  - May be asymptomatic

LG Endometrial Stromal Sarcoma

- 10-15% of uterine malignancies with a mesenchymal component
- 1/3 extrauterine pelvic extension at diagnosis
- Rarely presentation at metastatic site (often ovary)
- Staging following carcinoma FIGO staging
- Occasionally association with prolonged estrogenic stimulation, tamoxifen treatment, or prior pelvic irradiation

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA (WHO)

SHARED HISTOLOGIC APPEARANCE

Tumors composed of cells resembling those of the proliferative-phase endometrial stroma. Numerous thin-walled small arteriolar type vessels are characteristically present

DIFFERENTIAL HISTOLOGIC FEATURES

Myometrial and/or vascular invasion
**Endometrial Stromal Nodule**

**WHO definition**
- Unusual benign endometrial stromal tumor characterized by a well delineated expansile margin on microscopic examination
- Presence of focal irregularities in the form of lobulated or finger-like projections (< 3) into the adjacent myometrium that do not exceed 3 mm
- No vascular invasion

**REPORTING ENDOOMETRIAL STROMAL TUMORS IN CURETTAGE SPECIMENS**
- Adequate sampling of the tumor-myometrial interface is necessary in order to:
  1. evaluate the degree of infiltration of the tumor into the myometrium
  2. correctly classify the tumor
  3. properly treat the patient
- In 99.9% of cases, margins cannot be completely assessed in endometrial curettage
  - Working diagnosis should be EST

**Endometrial Stromal Sarcoma**

**Differential Diagnosis:**
- Cellular endometrial polyp
- Adenomyosis
  - with sparse glands / intravascular
- Highly cellular leiomyoma
- Highly cellular variant of intravenous leiomyomatosis

**Features of Highly Cellular Leiomyomas that Cause Confusion with Endometrial Stromal Tumors**
- Dense cellularity
- Prominent vascularity
- Irregular margin

**LOW-GRADE ENDOOMETRIAL STROMAL SARCOMA**

**Prognosis and treatment**
- Hysterectomy and bilateral oophorectomy
- 80-90% 5-year survival rate and 70% 10-year survival
- 5-year survival close to 100% and 10-year survival of 80-90% for stage I (organ confined)
- Hormonal treatment, aromatase inhibitors or radiation as other options
- Stage most powerful prognostic factor

**LOW-GRADE ENDOOMETRIAL STROMAL SARCOMA**

**Potential prognostic factors?**
- Even though low-grade endometrial stromal sarcomas are considered low-grade malignant tumors, still a number of patients with stage I disease develop recurrences or even die of disease
- Are there any pathologic parameters that can help to predict which tumors will behave in a more aggressive manner?
**LOW-GRADE ENDOMETRIAL STROMAL SARCOMA**

- Potential prognostic factors:
  - Age
  - Race
  - Size
  - Cytologic atypia
  - Mitotic activity
  - Ploidy

**PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS**


- 96 primary uterine corpus ESS
- 85 patients with stage I tumors
- Analysis of size, stage, and morphologic features including mitotic activity, degree of cytologic atypia, tumor cell necrosis, hemorrhage, inflammation, calcification, foam cells, cells with decidual features, epithelioid, glandular, or smooth muscle areas

**PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS**


- When evaluating mitotic activity they followed Norris and Taylor’s guidelines who divided ESS into low and high grade on the basis of finding < or ≥ 10 mitoses/10 high-power fields
- When evaluating cytologic atypia, all tumors with significant pleomorphism were excluded (following Evans work = tumors should show evidence of endometrial stromal differentiation)
- Nucleomegaly could not be greater than moderate, but still gave three grades

**ENDOMETRIAL STROMAL SARCOMAS (93)**

**Conclusions:**

- By univariate analysis and including all stages:
  - Patients with tumors showing ≥ 10 mitoses/10 HPFs had significantly less favorable survival
  - Increasing atypia was associated with an increasing relapse rate
- By multivariate analysis only stage was a significant predictor of recurrence and survival
- Mitotic index and cytologic atypia lost predictive value in stage I tumors
PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

- Pleomorphic undifferentiated sarcoma is a different clinicopathologic entity (as described by Evans)

- The main strategy for separating mitotically active, cytologically atypical endometrial stromal sarcomas that lack the arborizing stromal vasculature from undifferentiated sarcoma involves an assessment of nuclear pleomorphism

ENDOMETRIAL STROMAL SARCOMAS AND RELATED HIGH-GRADE SARCOMAS:
IMMUNOHISTOCHEMICAL AND MOLECULAR GENETIC STUDY OF 31 CASES

• Objective: Address the controversial nomenclature of non-low grade ESS (“Undifferentiated endometrial sarcoma”)

• 18 low-grade ESS, 7 UES-U (nuclear uniformity, but nucleomegaly, hyperchromatism and nucleoli), and 6 UES-P (nuclear pleomorphism)

ENDOMETRIAL STROMAL SARCOMAS AND RELATED HIGH-GRADE SARCOMAS:
IMMUNOHISTOCHEMICAL AND MOLECULAR GENETIC STUDY OF 31 CASES

<table>
<thead>
<tr>
<th></th>
<th>LG-ESS</th>
<th>UES-U</th>
<th>UES-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>13/17</td>
<td>2/7</td>
<td>2/6</td>
</tr>
<tr>
<td>DOD</td>
<td>0/13</td>
<td>3/7</td>
<td>3/5</td>
</tr>
<tr>
<td>ER</td>
<td>17/17</td>
<td>4/7</td>
<td>0/5</td>
</tr>
<tr>
<td>PR</td>
<td>17/17</td>
<td>4/7</td>
<td>0/5</td>
</tr>
<tr>
<td>β-catenin</td>
<td>8/17</td>
<td>6/7</td>
<td>2/6</td>
</tr>
<tr>
<td>JAZF1-JJAZ1 fusion</td>
<td>6/12</td>
<td>1/3</td>
<td>0/3</td>
</tr>
<tr>
<td>p53 mutations</td>
<td>0/17</td>
<td>0/7</td>
<td>3/7</td>
</tr>
</tbody>
</table>

SUMMARY

• Stage most important prognostic factor in low-grade ESS
• No other proved pathologic factors to predict recurrence in stage I low-grade ESS
UTERINE ADENOSARCOMA

W Glenn McCluggage

Department of Pathology, Royal Group of Hospitals Trust, Belfast, Northern Ireland.

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 extraterine 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 ≥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.

REFERENCES:

1 Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol 1990;21;363-381.
4 Seidman JD, Chauhan S. Evaluation of the relationship between adenosarcoma and carcinosarcoma and a hypothesis of the histogenesis of uterine sarcomas. Int J Gynecol Pathol 2003;22;75-82.
MESENCHYMAL TUMOURS OF THE UTERUS- USCAP, 2009

ADENOSARCOMA

W Glenn McCluggage,
Royal Group of Hospitals Trust,
Belfast, Northern Ireland

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
<table>
<thead>
<tr>
<th><strong>GROSS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• usually exophytic polypoid, sometimes lobulated lesions</td>
</tr>
<tr>
<td>• cut surface may be spongy with cystic spaces</td>
</tr>
<tr>
<td>• may be multiple polyps (beware recurrent endometrial/cervical polyps)</td>
</tr>
<tr>
<td>• tumour may protrude through external os</td>
</tr>
<tr>
<td>• occasional cases arise in myometrium, ‚from adenomyosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CLASSICAL DIAGNOSTIC FEATURES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• club-like/leaf-like/phyllodes-like</td>
</tr>
<tr>
<td>• bland epithelium of a variety of Mullerian types on surface and lining dilated or slit-like spaces</td>
</tr>
<tr>
<td>• cambium layer (stromal condensation)</td>
</tr>
<tr>
<td>• intraglandular stromal projections</td>
</tr>
<tr>
<td>• stromal hypercellularity</td>
</tr>
<tr>
<td>• stromal atypia and mitotic activity (especially in cambium layer)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PITFALLS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• may get large areas of bland mitotically inactive fibrous or myxoid stroma</td>
</tr>
<tr>
<td>• periglandular cuffing may be focal</td>
</tr>
<tr>
<td>• mitotic activity may be focal</td>
</tr>
<tr>
<td>• need to sample well</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GLANDULAR ELEMENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• may get focal proliferation with areas resembling hyperplasia or even endometrioid adenocarcinoma (histogenesis of small minority of carcinosarcomas)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MYOMETRIAL INVASION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• found in 15-20% of tumours</td>
</tr>
<tr>
<td>• usually superficial</td>
</tr>
<tr>
<td>• occasionally deep</td>
</tr>
<tr>
<td>• rarely get vascular invasion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MORE UNCOMMON FEATURES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• heterologous elements (rhabdomyoblasts, cartilage etc)</td>
</tr>
<tr>
<td>• smooth muscle differentiation</td>
</tr>
<tr>
<td>• sex cord-like elements</td>
</tr>
<tr>
<td>• angiosarcoma</td>
</tr>
<tr>
<td>• stromal decidualisation</td>
</tr>
</tbody>
</table>
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

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

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
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
MMMT (Carcinosarcoma)

Carcinosarcoma, also referred to as “malignant mixed Mullerian tumor” or “MMMT” is a neoplasm composed of malignant-appearing epithelial and mesenchymal elements (1). Although they can arise in any genital organ, they are found most frequently in the uterus where they represent less than 5% of malignant neoplasms. These tumors are increasingly thought of as carcinomas that demonstrate sarcomatoid differentiation (2-5), although many gynecologists persist in classifying them as sarcomas. Regardless, they are extraordinarily heterogeneous, clinically aggressive neoplasms. Their morphologic heterogeneity is responsible for difficulties in accurate diagnosis. A particular problem is the imprecise nature of the entity’s current definition. As will be discussed subsequently, there is a group of biphasic uterine neoplasms that have been historically considered carcinosarcomas. With the advent of carcinoma-style staging surgeries for CS, treatment with effective chemotherapeutic agents for high-risk and high-grade uterine malignancies, specific treatment protocols for CS, increased use of immunohistochemistry and advances in our understanding of the interplay of genetics, tumor biology and epidemiology, it has become clear that only a subset of lesions historically considered CS conform to most of the commonly held assumptions about what the typical CS should be: CSs, as a group, should be highly aggressive tumors, more clinically aggressive than carcinomas, and composed of malignant epithelial and mesenchymal elements. These are the guidelines that will be used to define CS in this presentation.

Clinical Features

The mean age of patients with endometrial carcinosarcoma is in the 7th decade, but the age range spans from the 4th through 9th decades. The disease tends to present like other endometrial cancers, with vaginal bleeding being common. Another typical presentation of carcinosarcoma is a polypoid mass that protrudes through the cervical os.

The 5-year survival for carcinosarcoma is around 30% and the 5 year survival in surgical stage I disease (confined to uterus) is approximately 50% (6-9). This very aggressive profile contrasts with that of other high grade endometrial cancers where 5 year survivals in stage I disease are approximately 80% or better (10, 10a). This has led to toxic treatment protocols that usually include ifosfamide and cisplatin along with whole pelvic irradiation. There are no data that suggest that treating the predominant tumor component (i.e. rhabdomyosarcoma, when present) is preferable to standard therapy.

There have been numerous studies that have sought to define prognostic factors in carcinosarcoma, but many are compromised by including at least 2 groups of patients,
some of whom were clinically staged and others who were comprehensively (i.e. surgically staged) (6-9). Pathologically determined prognostic features in clinically staged CS patients are generally the same as for patients with suboptimally staged endometrial carcinoma (grade, depth of invasion, presence of lymphovascular invasion). There is general agreement that surgical stage is the most important prognostic indicator regardless of how the patient was staged. In common with some of the older literature, our group has also recently found that the presence of heterologous elements is a statistically significant poor prognostic factor in comprehensively staged, FIGO stage I patients (11). 30% of patients with heterologous elements survive 5 years as compared to 80% of patients with homologous elements. Other factors that have been proposed include the grade of the carcinomatous and sarcomatous elements, the percentage of tumor demonstrating sarcomatous differentiation, the depth of myometrial invasion and the presence of lymphovascular invasion (6-9).

**Morphology**

The cardinal rule of carcinosarcoma is that it is a biphasic tumor, composed of distinctive and separate, but admixed, malignant-appearing epithelial and mesenchymal elements. The epithelial and mesenchymal elements should not merge with one another. This definition essentially excludes from consideration all monophasic tumors such as undifferentiated carcinomas and undifferentiated sarcomas and tumors that display either malignant-appearing epithelial elements (endometrioid adenocarcinoma with spindle cell features) or malignant-appearing mesenchymal elements (Mullerian adenosarcoma).

Carcinomatous and sarcomatous elements are generally easy to find, but occasional cases show sarcoma or carcinoma almost exclusively. About one-third of carcinosarcomas harbor a carcinoma with endometrioid differentiation and two-thirds contain carcinomas that are serous or high grade, not otherwise specified (11). The former tumors may be associated with complex atypical hyperplasia and endometrial intraepithelial carcinoma may be found in the latter tumors. Clear cell, mucinous and squamous carcinomas have also been described. In our series (11), 10% of the carcinomatous components were FIGO grade 1, 10% were grade 2 and 80% were grade 3. The sarcomatous components were heterogeneous. The homologous components of carcinosarcoma are usually spindle cell tumors without obvious differentiation; many resemble fibrosarcomas or pleomorphic sarcomas. In our experience, it is uncommon to find a carcinosarcoma containing areas that closely resemble leiomyosarcoma or endometrial stromal sarcoma. Almost all are histologically high grade. The most common heterologous elements are chondroid or rhabdomyoid (constituting something that resembles either pleomorphic rhabdomyosarcoma or embryonal rhabdomyosarcoma). Occasional cases showing lipoblastoid, osteoid, neural/neuroectodermal and angiomatoid elements have been described.

Most carcinosarcoma metastases are epithelial only or, less commonly, epithelial predominant. It is very uncommon to find sarcoma-only metastases from carcinosarcoma.
**Immunohistochemistry**

The immunophenotype of carcinosarcoma should closely follow that of the individual elements present in the tumor. For example, the serous component should express keratins and p53, while the rhabdomyoblastic component should express desmin and myogenin. It is a well known diagnostic pitfall that the sarcomatous component of carcinosarcoma can express keratins, but the same is true of leiomyosarcoma, in particular. Given this and the adherence to the cardinal rule of carcinosarcoma (see above), immunohistochemistry should not be needed for diagnosis and should only be used in exceptional circumstances. I essentially restrict the use of immunohistochemistry to cases where I want to support my impression of a heterologous element, particularly rhabdomyosarcoma. I will rarely perform immunohistochemistry to support my impression of a malignant epithelial component (p53 in epithelium that looks neoplastic and probably malignant) or to support a morphologically distinct epithelial component where the overwhelming impression is that of a monophasic undifferentiated tumor. Pleomorphic, monophasic neoplasms with patchy keratin expression should not necessarily be diagnosed as carcinosarcomas.

**Differential Diagnosis**

As mentioned earlier, most monophasic tumors should not be considered candidates for a carcinosarcoma diagnosis, although many pathologists believe that uterine pleomorphic rhabdomyosarcomas represent carcinosarcomas in which the epithelial component has not been sampled or has been overgrown by sarcoma. This leaves the biphasic tumors. The four most important biphasic tumors to consider in the differential diagnosis are adenosarcoma, endometrioid adenocarcinoma with spindle cell elements (12, 13), so-called dedifferentiated endometrial carcinoma (14, 15), and composite or collision tumors.

**Endometrioid adenocarcinoma with spindle cell elements versus carcinosarcoma**

Endometrioid adenocarcinoma with spindle cell elements has long been recognized, although it was only recently given a name and an in-depth description (12, 13). In this tumor, the endometrioid elements, frequently showing squamous metaplasia, fuse imperceptibly with spindle cell elements that are never histologically high grade. In most cases, the endometrioid component is no more than FIGO grade 2 and the spindle cell component is cellular and sometimes mitotically active, but not markedly atypical. If there is confusion between this entity and carcinosarcoma, use the tumor grade and the presence or absence of “element fusion” to inform the decision. Carcinosarcoma contains easily separable, high grade epithelial and mesenchymal elements whereas this type of endometrioid adenocarcinoma shows seamless fusion of two histologically low grade components (i.e. element fusion). Be aware here as well that endometrioid adenocarcinomas can contain chondroid and osteoid elements. Heterologous elements by themselves do not signify carcinosarcoma. FIGO grade 1 and 2 endometrioid carcinomas with spindle cell elements are thought to be clinically similar to low grade endometrioid carcinomas that lack spindle cell elements.
“Dedifferentiated” endometrial carcinoma vs carcinosarcoma

“Dedifferentiated” endometrial carcinoma is a recently described entity that includes a well or moderately differentiated endometrioid adenocarcinoma juxtaposed with an undifferentiated carcinoma (14, 15). In contrast to carcinosarcoma, the endometrioid component is usually well-differentiated; the undifferentiated component is made of sheets of small rounded cells of uniform size instead of spindle shaped or obviously pleomorphic cells. Glandular, nested and trabecular architecture are not encountered in the undifferentiated component. Squamous, mucinous and neuroendocrine differentiation are also lacking. The undifferentiated cells frequently have a rhabdoid appearance and may be deposited in a myxoid matrix (Altrabulsi, Malpica et al. 2005). The undifferentiated component may resemble lymphoma, plasmacytoma, myxoid chondrosarcoma, small cell carcinoma or even metastatic lobular carcinoma of the breast. These cells fail to express muscle-specific markers, including markers of skeletal muscle differentiation. The undifferentiated component characteristically shows only focal keratin expression, but nearly every case exhibits strong EMA (15) and cytokeratin 18 expression in a minority of cells. From a clinical standpoint, these tumors are probably even more aggressive than carcinosarcomas, with almost universal recurrences and deaths due to disease (14). Emerging data also suggest that, unlike CS, de-differentiated carcinomas frequently demonstrate an abnormal DNA mismatch repair gene expression profile that places some of them within the spectrum of tumors encountered among patients with Lynch Syndrome/Hereditary Non-polyposis Colorectal Carcinoma Syndrome (18).
MMMT (Carcinosarcoma) references


Carcinosarcoma/MMMT
International Society of Gynecological Pathologists
USCAP Companion Meeting 2009
Boston, MA

Robert Soslow, M.D.
Memorial Sloan-Kettering Cancer Center

Carcinosarcoma

• WHO definition:
  – Neoplasm composed of an admixture of malignant epithelial and mesenchymal components

CS, as diagnosed historically, is an extremely heterogeneous entity

Carcinosarcoma

• <5% of all uterine tumors
• Median age--65 years
• Symptoms/signs: bleeding, abdominal pain, polyp
• Diagnosis: bx/curettage, hysterectomy
• Staging: like endometrial cancer
• Epidemiology: may occur following pelvic irradiation, tamoxifen

Carcinosarcoma

– Overall survival is ~35%--adjuvant therapy
  • ~50% survival stage I
  • 0-25% survival >stage II

Stage is the most important prognostic factor

Carcinosarcoma

– Clinical versus surgical staging
  – Other prognostic features:
    • Depth of invasion
    • Lymphovascular invasion
    • Tumor size
    • Sarcoma histology
    • Carcinoma histology and grade
Stage I carcinosarcoma study

- WHO criteria, excluding:
  - Monophasic tumors with an epithelial/mesenchymal immunophenotype


Stage I carcinosarcoma study

- WHO criteria, excluding:
  - Monophasic tumors
  - Biphasic tumors containing carcinoma without a definitive mesenchymal component


Stage I carcinosarcoma study

- WHO criteria, excluding:
  - Monophasic tumors
  - Biphasic tumors without a mesenchymal component
  - Biphasic tumors other than CS


Stage I carcinosarcoma study

- WHO criteria, excluding:
  - Monophasic tumors
  - Biphasic tumors without a mesenchymal component
  - Biphasic tumors other than CS
  - Biphasic tumors that are reportedly less aggressive than CS


Stage I carcinosarcoma study

- 47 surgically staged patients

- Pathologic features of possible prognostic significance
  - Tumor size
  - Myometrial and lymphovascular invasion
  - Grade, type and prevalence of epithelial and mesenchymal components
    • Heterologous vs homologous


Carcinosarcoma vs high-grade endometrial adenocarcinoma

- 0.0 0.2 0.4 0.6 0.8 1.0
- 0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
- Months from Date of Diagnosis

**Carcinosarcoma vs high-grade endometrial adenocarcinoma**

- FIGO stage I CS with heterologous elements are highly aggressive (as aggressive as pure rhabdomyosarcoma)
- FIGO stage I CS without heterologous elements are no more aggressive than high grade endometrial carcinomas

**Carcinosarcoma (CS)**

- FIGO stage I CS with heterologous elements are highly aggressive (as aggressive as pure rhabdomyosarcoma)
  - Sarcoma-like?
- FIGO stage I CS without heterologous elements are no more aggressive than high grade endometrial carcinomas
  - Carcinoma-like?

**Differential diagnosis**

- Adenosarcoma
- Endometrioid carcinoma with spindle cell elements
- "Dedifferentiated endometrial carcinoma"
- Combined adenocarcinoma and neuroendocrine carcinoma
- Collision tumors

**Heterologous CS vs Rhabdomyosarcoma**

**Carcinosarcoma (CS)**

- FIGO stage I CS with heterologous elements are highly aggressive (as aggressive as pure rhabdomyosarcoma)
  - Sarcoma-like?
- FIGO stage I CS without heterologous elements are no more aggressive than high grade endometrial carcinomas
  - Carcinoma-like?

**De-differentiated endometrial carcinoma**

- Well- or moderately-differentiated endometrioid carcinoma juxtaposed with an undifferentiated carcinoma
- Endometrium>>ovary
  - Synchronous or metachronous
- Prognosis: 20/21 patients DOD or AWD

Undifferentiated component

- Morphology:
  - Small, round cells; not overtly pleomorphic
  - Solid sheets; no glands, no squamous
  - Myxoid stroma and rhabdoid cells
- Immunohistochemistry:
  - Relative loss of pan-keratin and ER/PR
  - EMA, CK18 retained in minority of cells
  - Minor neuroendocrine marker expression allowed


Algorithm study: secondary observations

- DNA MMR loss correlated with:
  - Personal and family history of relevant cancers
  - Lower uterine segment tumors
  - Synchronous tumors (ovarian clear cell; endometriosis-associated; colorectal)
  - De-differentiated carcinoma (5/27)
    - MLH1/PMS2 (3); MSH2/6 (2)

Garg K, et al. Mod Pathol 2008;21 (supplement 1):205A

Biphasic tumor overview

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Mechanism</th>
<th>Spread</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Undiff</td>
<td>?cell adhesion</td>
<td>Like carcinoma</td>
<td>Dismal</td>
</tr>
<tr>
<td>LG</td>
<td>LG spindle cell</td>
<td>?</td>
<td>Like LG carcinoma</td>
<td>Favorable</td>
</tr>
<tr>
<td>HG</td>
<td>HG spindle cell (homologous)</td>
<td>EMT</td>
<td>Like HG carcinoma</td>
<td>Guarded</td>
</tr>
<tr>
<td>HG</td>
<td>HG spindle cell (heterologous)</td>
<td>EMT</td>
<td>Like HG carcinoma</td>
<td>Highly unfavorable</td>
</tr>
</tbody>
</table>

*DNA mismatch repair abnormalities/MSI-H

Summary

- Homologous CS—like high grade carcinoma
- Heterologous CS—like rhabdomyosarcoma
- EC with spindle cells—like FIGO grade 1 or 2 carcinoma
- Dedifferentiated EC—like high grade carcinoma, but worse