Pathology of Uterine Sarcomas

11

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Introduction

Uterine sarcomas are a rare, heterogeneous group of neoplasms, which account for approximately 1 % of all female genital tract malignancies and 3–5 % of malignant uterine tumors [1]. The tumors are derived from the mesenchymal components of the uterus, consisting of endometrial stroma, smooth muscle and blood vessels, or admixtures of these (referred to as homologous elements). Rarely the tumors may contain tissue types not normally seen in the uterus, such as striated muscle, cartilage, or bone (referred to as heterologous elements). Compared with the more common endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis with a high rate of local recurrence and/or metastasis. The lack of consensus, on treatment options and risk factors for poor outcome, is largely due to the rarity of these tumors and their histopathological diversity. The classification and staging of these tumors were revised in 2013 and 2009, respectively.

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Classification

Historically uterine sarcomas have been classified into carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, undifferentiated sarcoma, and a heterogeneous group of vascular, lymphatic, and heterologic sarcomas. Recently, carcinosarcoma has been reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma. Despite this, and probably because it behaves more aggressively than the ordinary endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas[2].

A simple classification of uterine sarcomas based on 2014 WHO Classification of Tumors of Female Reproductive Organs [3] is shown in Table 11.1.

A practical classification of uterine sarcomas excluding carcinosarcoma, with incidence [4], is as follows:

Leiomyosarcoma (LMS 60 %)
Endometrial stromal sarcoma (ESS 30 %)
Undifferentiated uterine sarcoma (UUS 5%)
Adenosarcoma and other uterine sarcomas (5 %)

The 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria for endometrial carcinoma have been used until now for staging uterine sarcomas in spite of the different biologic behavior of both tumor categories. The new FIGO staging system, approved by the FIGO

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Table 11.1 Classification of uterine sarcomas

Endometrial stromal and related tumors
Low-grade endometrial stromal sarcoma
High-grade endometrial stromal sarcoma
Undifferentiated uterine sarcoma
Uterine tumor resembling ovarian sex cord tumor (UTROSCT)
Smooth muscle tumors
Leiomyosarcoma
Epithelioid variant
Myxoid variant
Smooth muscle tumor of uncertain malignant potential
Mixed epithelial and mesenchymal tumors
Adenosarcoma
Carcinosarcoma
Miscellaneous mesenchymal tumors
Rhabdomyosarcoma
Perivascular epithelioid cell tumor ("PEComa")
Other malignant mesenchymal tumors

executive board in September 2008, is specifically designed for uterine sarcomas to reflect different biologic behavior [5]. It includes: (1) staging for leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), (2) staging for adenosarcomas (AS), and (3) staging for carcinosarcomas, of which the first two are new, while carcinosarcomas will continue to be staged according to the new classification of endometrial carcinoma.

FIGO Staging System for Uterine Sarcomas (2009)

1. Leiomyosarcomas and endometrial stromal sarcoma

Stage I Tumor limited to uterus
IA Less than or equal to 5 cm
IB More than 5 cm
Stage II Tumor extends beyond the uterus, within the pelvis
IIA Adnexal involvement
IIB Tumor extends to extrauterine pelvic tissue
Stage III Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA One site
IIIB More than one site
IIIC Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV
IVA Tumor invades bladder and/or rectum
IVB Distant metastasis

2. Uterine adenosarcomas

Stage I Tumor limited to uterus
IA Tumor limited to endometrium/endocervix with no myometrial invasion
IB Less than or equal to half myometrial invasion
IC More than half myometrial invasion
Stage II Tumor extends beyond the uterus, within the pelvis
IIA Adnexal involvement
IIB Tumor extends to other pelvic tissues
Stage III Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA One site
IIIB More than one site
IIIC Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV
IVA Tumor invades bladder and/or rectum
IVB Distant metastasis

3. Carcinosarcomas

Carcinosarcomas should be staged as carcinomas of the endometrium.

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

The 2009 FIGO staging systems make no mention of undifferentiated uterine sarcoma or pure heterologous sarcomas, such as rhabdomyosarcoma. These tumors are staged in the same way as leiomyosarcoma and endometrial stromal sarcoma. The term "uterus" includes the uterine corpus and uterine cervix, and the 2009 FIGO staging system is used for all uterine sarcomas, irrespective of whether tumors arise in the corpus or cervix.

Leiomyosarcoma

Leiomyosarcomas are malignant neoplasms that demonstrate either histological or immunohistochemical smooth muscle differentiation. Although

LMSs represent only about 1 % of all uterine malignancies, they are the most common pure uterine sarcomas accounting for 25–30 % of uterine sarcomas. They occur almost exclusively in adults and in an older age group than leiomyomas, with the median age being 50–55 years. LMSs are aggressive tumors that have a tendency to spread locally, regionally, or by hematogenous dissemination, most commonly to the liver and lung. The most common presenting symptoms are abnormal vaginal bleeding and pelvic pain. Local and regional spread may produce an abdominal or pelvic mass with gastrointestinal or urinary tract symptoms or hemoperitoneum. LMSs are generally thought to arise *de novo*, but recent molecular genetic evidence suggests that some of these tumors may evolve from preexisting leiomyomas [6].

Gross Features

LMSs are characteristically solitary, intramural masses and are usually not associated with leiomyomas. The gross appearance of LMSs has significant differentiating features from that of leiomyomas in most of the cases. They are large tumors averaging 10 cm in diameter with poorly circumscribed borders that appear to irregularly infiltrate the adjacent myometrium. Leiomyomas, on the other hand, characteristically have a sharp line of demarcation separating the tumor from the myometrium. LMSs that present as a circumscribed mass are not usually recognized grossly as a malignant tumor because of the overlap in appearance between malignant change and the various forms of degeneration. The macroscopic features that are suspicious of malignancy and require thorough sampling of the tumor are: loss of whorled pattern, heterogeneity, irregular, merging, blurred or poorly defined margins, yellow, tan or gray color, softer tumors that lack a rubbery, resilient feel, and absence of a bulging surface. The cut surface may also show irregular areas of hemorrhage and necrosis.

Microscopic Features

LMSs exhibit hypercellularity, severe nuclear atypia, geographic foci of tumor cell necrosis, and a high mitotic rate including atypical mitotic figures, generally exceeding 15 mitotic figures per 10 high-power fields (Fig. 11.1a). Mitosis is counted in the most mitotically active areas in ten successive HPFs using an 40× objective and a standard 10× eyepiece. The poorly differentiated tumors show nuclear pleomorphism, hyperchromasia, prominent nucleoli, and tumor giant cells, features that indicate increasing anaplasia of the tumor (Fig. 11.1b). Well-differentiated LMS on the other hand consist of elongated smooth muscle cells with regular nuclei that differ little from those of a leiomyoma (Fig. 11.1c). Areas of coagulative necrosis and hemorrhage are seen (Fig. 11.1d). The tumors, in most cases, would have invaded the adjacent myometrial tissue at the time of diagnosis and may have perforated the serosal surface of the uterus with involvement of other pelvic organs. Vascular invasion may also be seen.

If a smooth muscle tumor is well circumscribed, composed of cells that are uniform in size and shape, has no intravascular component, cytological atypia or necrosis, and with a mitotic count of less than 5 mitotic figures per 10 HPFs, then the tumor is a leiomyoma. On the other hand, when a tumor has infiltrative margins (Fig. 11.1e), intravascular growth, marked cytological atypia, coagulative tumor cell necrosis, a mitotic count greater than 10 mitosis per 10 HPFs and abnormal mitotic figures, then the tumor is an LMS. Most of the smooth muscle tumors belong to the two extremes of the spectrum and are either clearly benign or malignant. It is the tumors that fall in the intermediate category that require careful consideration to reliably categorize them, to predict prognosis, and to decide on further treatment. Numerous studies have been undertaken during the past three decades to define the histological criteria that would help to correctly categorize these tumors and to differentiate them from leiomyomas with atypical histological features like the mitotically active leiomyoma, cellular leiomyoma, atypical leiomyoma, myxoid leiomyoma, epithelioid leiomyoma, hemorrhagic leiomyoma, leiomyoma with hormone-induced changes, and from leiomyomas with unusual growth patterns like disseminated peritoneal leiomyomatosis, benign metastasizing leiomyoma, intravenous leiomyomatosis, and lymphangioleiomyomatosis. Of the

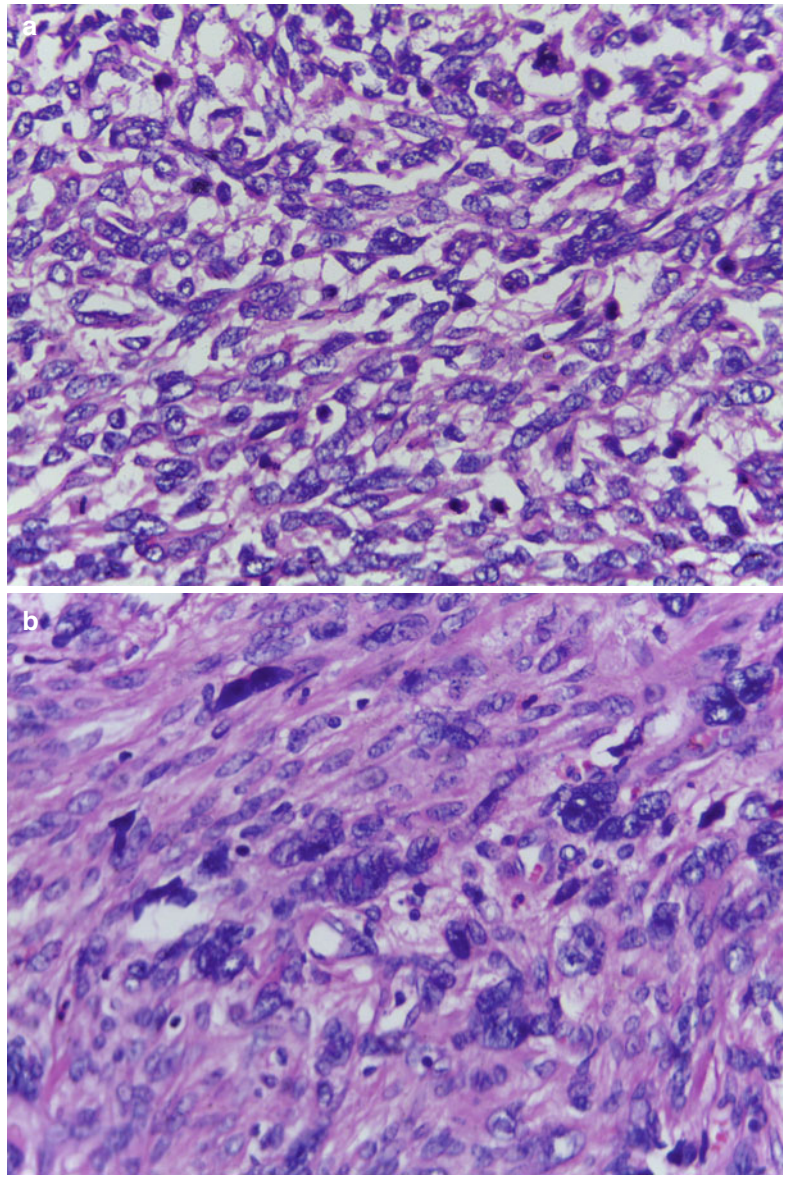
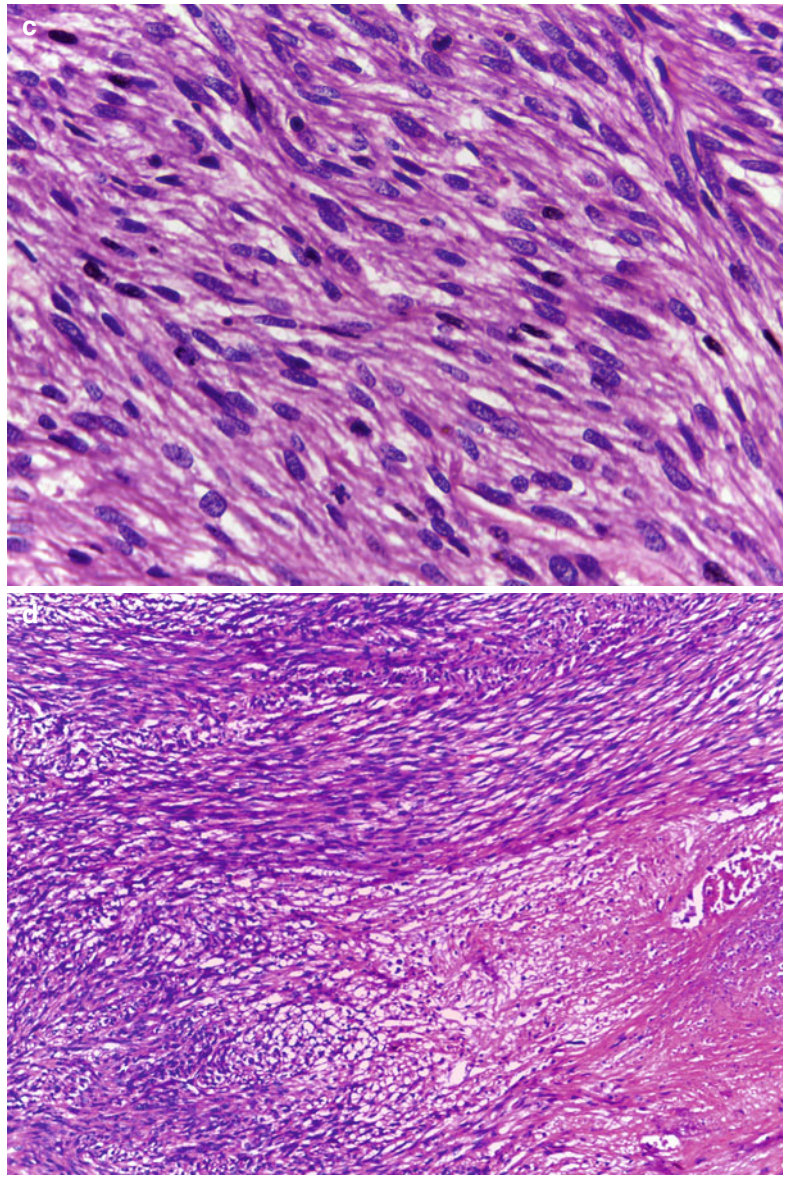


Fig. 11.1 (**a**) Leiomyosarcoma with hypercellularity, hyperchromatism, nuclear atypia, and high mitotic activity. (**b**) Leiomyosarcoma with nuclear pleomorphism and tumor giant cells. (**c**) Leiomyosarcoma with mild nuclear atypia and high mitotic activity. (**d**) Leiomyosarcoma with foci of coagulative necrosis. (**e**) Leiomyosarcoma with infiltrative margins



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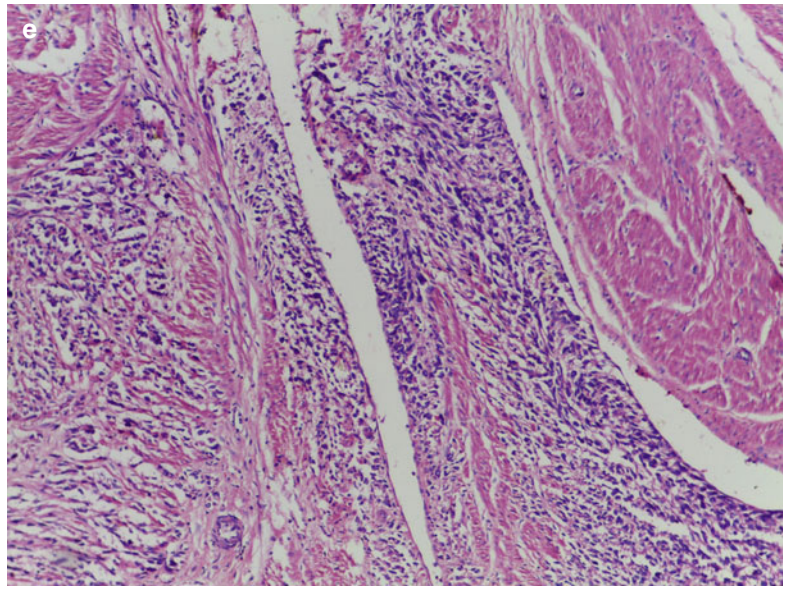

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many histological features that were assessed, mitotic index, the degree of cytological atypia, and the presence or absence of coagulative tumor cell necrosis have emerged as the most important predictors of behavior [7]. No single histological feature, with the exception of tumor cell necrosis, is diagnostic of malignancy. By employing three variables in the assessment of smooth muscle tumors, this diagnostic strategy moves away from complete dependence on mitotic count [8].

Other features that need to be considered are age of the patient, the size of the tumor and its gross appearance, the tumor's margins, and presence of vascular invasion.

The epithelioid and myxoid variants of LMS are rare tumors that exhibit malignant biologic behavior despite low mitotic counts and mild nuclear atypia.

LMSs are immunoreactive to smooth muscle markers such as smooth muscle actin, desmin, and h-caldesmon and histone deacetylace. Epithelioid LMS can express epithelial markers such as keratin and epithelial membrane antigen and are often immunoreactive to CD10.

Mutation and over expression of p53 and p16 has been described in a significant minority of LMS and in STUMPs that are at an increased risk of aggressive behavior but not in leiomyomas [9]. However other studies have shown that there is significant overlap in the Ki-67, p16, and p53 expression patterns in the atypical leiomyoma to LMS spectrum precluding its routine use for diagnostic purpose.

Smooth Muscle Tumor of Uncertain Malignant Potential

Uterine smooth muscle tumors that show some worrisome histological features like necrosis, nuclear atypia, or mitosis, but do not meet all the generally applied diagnostic criteria for LMS, fall into the category of STUMP. Tumors are categorized as STUMP when: (a) The tumor has a moderately high mitotic count and some nuclear atypia, but it is not clear whether the tumor belongs to the usual, myxoid, or epithelioid type, making it difficult to apply the relevant guidelines to determine malignancy. (b) The tumor exhibits diffuse significant atypia, but the mitotic index is borderline between atypical and malignant categories. (c) The tumor is hypercellular, lacks tumor cell necrosis, has an MI >10, and exhibits borderline nuclear atypia. (d) The tumor

has focal significant atypia, MI > 10, and no tumor cell necrosis. (e) Tumor cell necrosis is present in a hypercellular neoplasm, but there is no significant atypia and the mitotic index is <10. (f) The tumor has diffuse significant atypia or a MI >10, and has necrosis of ambiguous type [10]. When the differential diagnosis is between STUMP and LMS, the diagnosis of STUMP should be favored when the tumor is small (<3 cm), since malignant behavior in a primary smooth muscle tumor <3 cm is yet to be reported. A STUMP diagnosis in a myomectomy specimen allows for flexibility in management that would not be available to patients with a diagnosis of LMS. However, the term should be used sparingly and every effort should be made to classify a smooth muscle tumor into a specific category.

Diagnostic Criteria for Smooth Muscle Tumors [11]

Spindle Cell Smooth Muscle Tumors with Significant Nuclear Atypia

Diffuse or multifocal moderate – severe nuclear atypia + no tumor cell necrosis +>10 mitotic figures/10 high-power fields = Leiomyosarcoma

Diffuse, multifocal, or focal moderate – severe nuclear atypia + tumor cell necrosis +>10 mitotic figures/10 high-power fields = Leiomyosarcoma

Diffuse, multifocal, or focal moderate – severe nuclear atypia + no tumor cell necrosis +< 7 mitotic figures/10 high-power fields = Atypical leiomyoma

Diffuse or multifocal moderate – severe nuclear atypia + no tumor cell necrosis +>7 but < 10 mitotic figures/10 high-power fields = STUMP

Spindle Cell Smooth Muscle Tumors without Significant Nuclear Atypia

No or minimal nuclear atypia + tumor cell necrosis + > 10 mitotic figures/10 high-power fields = Leiomyosarcoma

No or minimal nuclear atypia + tumor cell necrosis +< 10 mitotic figures/10 high-power fields = STUMP

No or minimal nuclear atypia + no tumor cell necrosis +>5 but < 15 mitotic figures/10 high-power fields = Mitotically active leiomyoma

No or minimal nuclear atypia + no tumor cell necrosis + > 15 mitotic figures/10 high-power fields = Mitotically active leiomyoma (uncertain behavior)

Myxoid Smooth Muscle Tumors

<2 mitotic figures/10 high-power + no tumor cell necrosis + no to minimal nuclear atypia + no infiltration of myometrium = Myxoid leiomyoma

>2 mitotic figures/10 HPFs or tumor cell necrosis or moderate to severe nuclear atypia or infiltration of the myometrium = Myxoid leiomyosarcoma

Epithelioid Smooth Muscle Tumors

<3 mitotic figures/10 high-power fields + no tumor cell necrosis + no to minimal nuclear atypia + no vascular invasion + well circumscribed margin = Consider epithelioid leiomyoma

>3 mitotic figures/10 high-power fields or tumor cell necrosis or moderate to severe nuclear atypia or vascular invasion or infiltrative margin = Epithelioid leiomyosarcoma

Endometrial Stromal Sarcoma

Endometrial stromal tumors are rare tumors derived from the endometrial stromal cells and are composed of cells resembling proliferative phase endometrial stroma. The tumors are currently classified by the WHO as endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal

sarcoma, and undifferentiated uterine sarcoma. The tumors account for approximately 0.2 % of all malignant uterine tumors and 10–15 % of uterine sarcomas.

Malignant endometrial stromal tumors were subclassified for many years into low-grade and high-grade ESSs according to their degree of mitotic activity. Tumors with <10 mitotic figures per 10 high-power fields were low grade and tumors with >10 mitotic figures per 10 high-power fields were high grade. However, subsequent studies of uterine sarcomas with recognizable endometrial stromal differentiation failed to confirm the prognostic relevance of this separation based upon mitotic activity, and found surgical stage to be the most powerful predictor of clinical outcome [12]. This resulted in the elimination of the high-grade ESS category based upon a high mitotic rate, and the low-grade ESS were referred to simply as ESS. However, many investigators favored the acceptance of a category of ESS with more than the usual degree of nuclear atypia seen in low-grade ESS and with significant mitotic activity yet retaining some evidence of endometrial stromal differentiation. More recently, some tumors previously considered to be undifferentiated uterine sarcomas have been shown to be of endometrial stromal derivation (often associated with a component of low-grade endometrial stromal neoplasm) and are designated high-grade endometrial stromal sarcomas. The 2014 WHO classification of tumours of the uterine corpus includes the category of high-grade endometrial stromal sarcoma in the endometrial stromal and related tumors group [3].

Significant myometrial invasion and angiolymphatic invasion are the features that distinguish ESSs from ESNs. Patients are usually under 50 years of age and present with abnormal vaginal bleeding or pelvic or abdominal pain.

Gross Features

The tumors are solitary, well-delineated, and predominantly intramural lesions, but extensive myometrial permeation is common with extension to the serosa in approximately half of the cases. They may also present as endometrial polyps or involve both the endometrium and myometrium. Extrauterine primary ESS are also seen and often arise from foci of endometriosis. The tumors are fleshy and yellow or tan, bulging above the adjacent myometrium and lacking the whorled appearance of smooth muscle tumors. Cystic and myxoid degeneration as well as necrosis and hemorrhage are seen occasionally. Some tumors may infiltrate the myometrium with a worm-like appearance. The high-grade tumors usually present as intracavitary polypoid and/or intramural masses and often show extrauterine extension at the time of diagnosis.

Microscopic Features

Low-grade ESS is usually a densely cellular tumor composed of diffuse sheets of uniform, round, oval to spindle-shaped cells of endometrial stromal type. The tumor cells lack significant atypia and pleomorphism (Fig. 11.2a). ESS is a low-grade tumor by definition and mitotic activity is usually low but may be high with mitotic rates of 10 or more per 10 high-power fields. However, the mitotic count is not a criterion for diagnosis. The tumors are supported by a characteristic vasculature composed of a rich network of regularly spaced, thin-walled, elongated, compressed, branching capillaries, and small arterioles resembling the spiral arterioles of the late secretory endometrium (Fig. 11.2b). The arterioles may be surrounded by concentric whorls of tumor cells (Fig. 11.2c). The tumors may have edematous, hyalinized, myxoid, or fibrous areas, clusters of foam cells, rhabdoid cells, endometrial-type glands, and even sex cord-like structures. Focal smooth muscle differentiation may be seen, but is less than 30 % of the tumor. When the smooth muscle component is 30 % or more, the tumors are designated mixed endometrial stromal and smooth muscle tumor. Rarely skeletal muscle, fat, or pseudo cartilage may be seen leading to problems in differential diagnosis.

The term, endolymphatic stromal myosis was formerly used for ESSs with a characteristic type

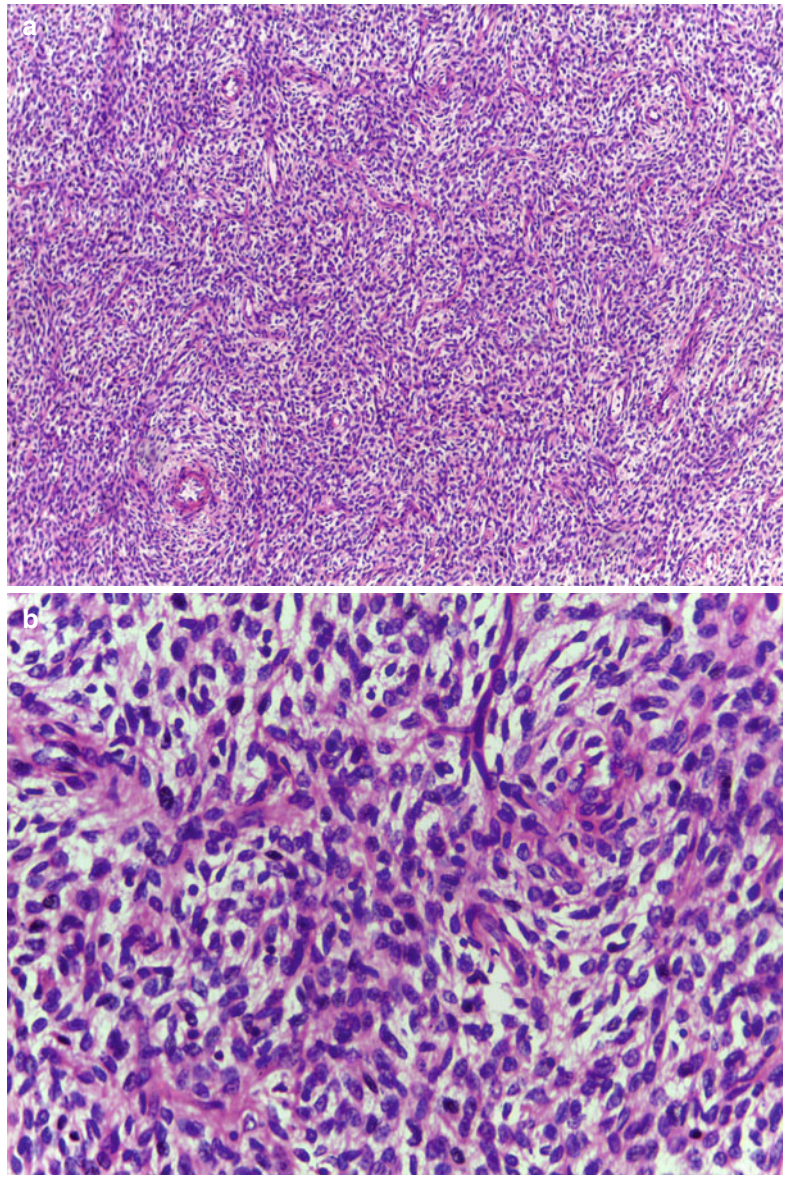


Fig. 11.2 (**a**) Endometrial stromal sarcoma with uniform cells resembling endometrial stromal cells. (**b**) Endometrial stromal sarcoma with rich vascular network. (**c**) Endometrial stromal sarcoma with perivascular whorls of tumor cells and rhabdoid cells

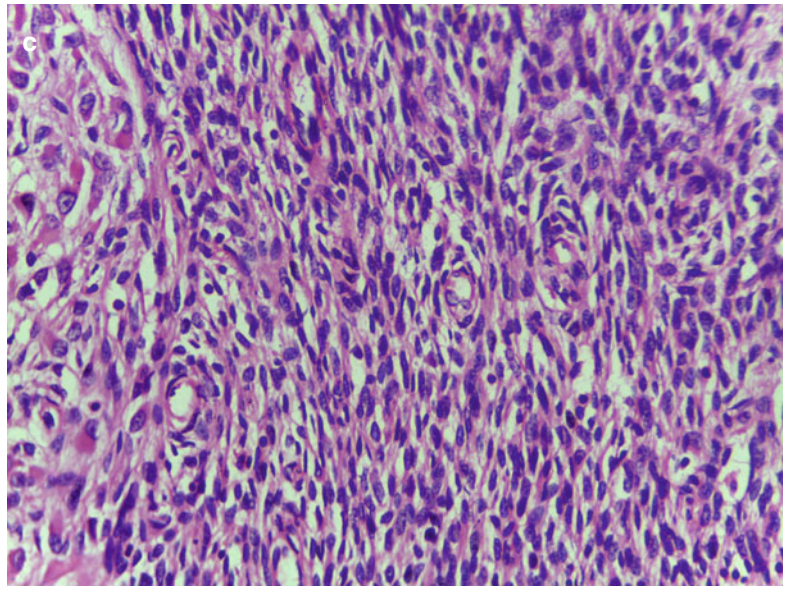


Fig. 11.2 (continued)

of infiltration. In these tumors, broad, rounded bands and serpentine processes of stromal cells infiltrated extensively into the myometrium, between the muscle fibers and particularly into the lymphatic and vascular spaces, sometimes with extension into vessels outside the uterus.

Although the high-grade endometrial sarcomas on low-power examination may reveal a similar pattern of infiltrative growth and vasculature to low-grade endometrial stromal sarcoma, these tumors typically have a confluent, permeative and destructive growth pattern with deep myometrial invasion. There is usually brisk mitotic activity and necrosis. A subset of these tumors displays specific morphological features and genetic abnormalities. There are usually two morphologically distinctive components in these tumors. A (usually predominant) high-grade, round cell tumor component is present in association with a low-grade spindle cell component with fibromyxoid features. The low-grade component is not present in all cases. The high-grade round cell component may be noncohesive or may have a nested, pseudopapillary or pseudoglandular appearance, or rhabdoid morphology.

ESS is immunoreactive to vimentin, CD10, focally for muscle specific actin, alpha smooth-muscle actin, and frequently keratin. They are usually negative for desmin and h-caldesmon. CD10 should not be used in isolation when evaluating the cell of origin in a uterine mesenchymal tumor since smooth muscle tumors, mixed Mullerian tumors, and even rhabdomyosarcomas are immunoreactive to CD10. Low-grade ESSs are usually positive for estrogen and progesterone receptors [13]. ESS often carry the translocation t (7; 17) with involvement of two zinc finger genes, *JAZF1 and JJAZ1*, suggesting a genetic basis for tumor development [14]. The fusion gene product can be detected by fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction.

A distinctive form of high-grade stromal sarcoma, having round cell morphology and a unique t(10;17)(q22;p13), which results in *YWHAE-FAM22* gene fusion, has recently been characterized and is associated with an aggressive clinical course [15]. In this newly described subset of high-grade endometrial stromal sarcoma, the high-grade component is typically CD10, ER, and PR negative, and shows variable, but often high, expression of cyclin D1. The high-grade component is also sometimes CD99 and CD117 (c-Kit) positive but DOG1 negative.

The associated low-grade component is usually, but not always, CD10, ER, and PR positive, negative with CD99 and CD117 and exhibits low expression of cyclin D1.

The differential diagnosis includes ESN, intravenous leiomyomatosis, adenomyosis with sparse glands, and adenosarcoma. ESS is distinguished from ESN by the nature of the interface with the surrounding myometrium. ESS is an infiltrative neoplasm while ESN is well circumscribed, although slight marginal irregularity is allowable. Vascular invasion excludes ESN. Adenomyosis with stromal predominance or adenomyosis with sparse glands may be misdiagnosed as ESS. Further sampling usually demonstrates areas with the typical adenomyosis with glands surrounded by hypertrophied myometrial smooth muscle. **It is difficult to distinguish an ESS from the above lesions in a biopsy or curettage.**

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcoma is the term currently used by the WHO for those rare sarcomas without smooth muscle or stromal differentiation and that have a more aggressive histologic appearance than allowed for ESS, but whose topography indicates an endometrial origin. These tumors are formed of anaplastic cells which have no recognizable evidence of a definite endometrial stromal phenotype [16].

UUSs generally occur in postmenopausal women, accounting for approximately 5 % of uterine sarcomas, present with abnormal vaginal bleeding and uterine enlargement, and are associated with a poorer prognosis.

Gross Features

UUSs are usually bulky, polypoid, intracavitary, fleshy, grayish-white tumors with areas of hemorrhage and necrosis. The aggressive growth pattern of UUS typically replaces the myometrium. Angiolymphatic invasion is often present, but the macroscopic plugs of intravascular tumor that are often seen in low-grade ESS are not seen in UUS.

Microscopic Features

The tumors lack the characteristic vascular pattern of low-grade ESS, and the tumor cells bear no resemblance to endometrial stromal cells. The tumor grows as cellular sheets, shows marked nuclear atypia and high mitotic activity, almost always exceeding 10MF/10HPF and sometimes up to 50MF/10HPF, with atypical mitotic figures and/or tumor cell necrosis, resembling the sarcomatous component of carcinosarcomas (Fig. 11.3a, b). Thorough sampling is essential to look for carcinomatous elements to rule out carcinosarcoma and to exclude poorly differentiated or undifferentiated carcinoma, leiomyosarcoma, rhabdomyosarcoma, large cell lymphoma, and granulocytic sarcoma – tumors that have to be considered in the differential diagnosis of an undifferentiated malignant tumor and are excluded by a combination of morphological and immunohistochemical features.

Recent studies suggest that UUS is a heterogeneous group and include a subgroup with uniform nuclei, and having morphologic, immunohistochemical, and genetic features more like low-grade ESS. These findings have reintroduced the term high-grade endometrial stromal sarcoma for those tumors whose cytologic atypia marginally exceeds the limits of that expected for low-grade ESS, exhibit high mitotic activity, including atypical mitotic figures, but still retain some evidence of endometrial stromal differentiation. UUSs are not immunoreactive with ER and PR but a high proportion is EGFR and p53 positive. Smooth muscle markers and myogenin or myoD1 may be used to rule out leiomyosarcoma or rhabdomyosarcoma respectively, or to identify a rhabdomyosarcomatous component of a carcinosarcoma.

The tumors have a poor prognosis and most patients die of disease within 2 years of the diagnosis. Vascular invasion, local recurrence, and distant metastasis are associated with a high mortality.

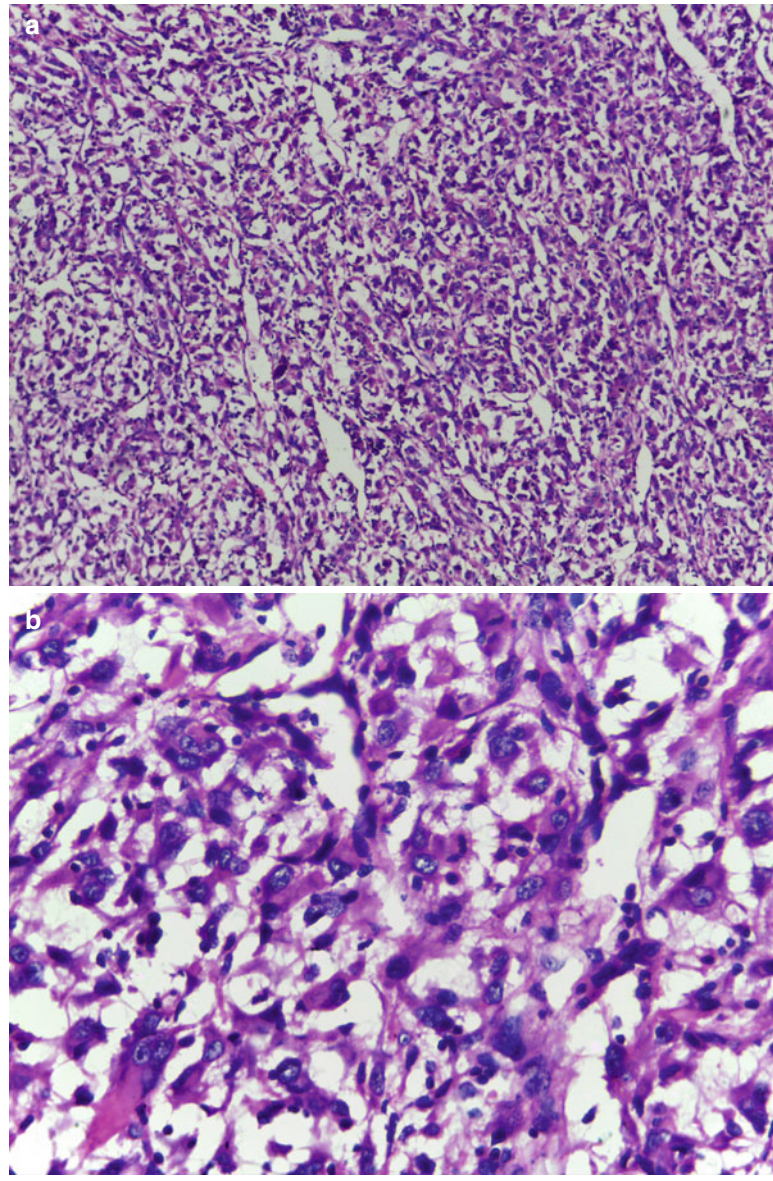


Fig. 11.3 (**a**) Undifferentiated uterine sarcoma resembling the sarcomatous component of carcinosarcomas, LP view. (**b**) Undifferentiated uterine sarcoma, HP veiw

Adenosarcoma

Adenosarcoma is a biphasic neoplasm composed of a benign epithelial component and a sarcomatous mesenchymal component**.** It is a rare tumor that accounts for only about 8 % of uterine tumors with a malignant mesenchymal component. Adenosarcomas are tumors of low malignant potential with distinctive clinicopathological features**.** The tumors occur in women across a wide age range, but mainly in postmenopausal women**.** They present with abnormal uterine bleeding related to a large polypoid tumor (mean diameter of 5 cm) that projects into the endometrial cavity and may protrude through the external os. Patients with repeated episodes

of recurrent endometrial polyps have to be carefully evaluated for the possibility of adenosarcoma, since areas with nondiagnostic or subtle histologic features are common [17]. Adenosarcomas have been reported in women undergoing tamoxifen therapy for breast cancer and occasionally after prior pelvic radiation. There is no association of adenosarcoma with obesity or hypertension.

Gross Features

Adenosarcomas typically grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the endocervix and within the myometrium, from foci of adenomyosis. The tumor may sometimes present as multiple papillary masses protruding into cystic spaces. On sectioning, the surface is tanbrown with foci of hemorrhage and necrosis. Small cysts are frequently present imparting a spongy appearance to the tumor. Most adenosarcomas do not invade the myometrium.

Microscopic Features

On low magnification, the tumor presents a leaf-like pattern closely resembling phyllodes tumor of the breast. The glands form elongated slit-like clefts resembling outlines of leaves, due to compression by polypoid projections of sarcomatous stroma (Fig. 11.4a–c). There is characteristic stromal condensation surrounding the cystic or cleft-like glands. It is in these areas that the stroma shows the greatest degree of atypia or mitotic activity. The glands are usually lined by endometrioid epithelium but may show focal metaplastic changes with mild atypia. The mesenchymal part of adenosarcoma is usually a low-grade homologous stromal sarcoma with varying amounts of fibrous tissue and smooth muscle. Heterologous elements are identified in approximately 10–15 % of cases consisting of striated muscle, cartilage, fat, and other components. Sex cord-like elements resembling those in endometrial stromal sarcoma are found in less than 10 % of adenosarcomas. Typically, mitotic figures are low (usually more than 1 per 10 high-power fields in the hypercellular cuffs) in the mesenchymal component, and cytological atypia is usually mild but occasionally may be moderate. The diagnosis of sarcomatous overgrowth is made when the pure sarcomatous component, usually of high grade, occupies 25 % or more of the total tumor volume. These areas of pure sarcoma are much more likely to exhibit higher nuclear grade with increased mitotic activity and higher Ki-67 proliferation index, more tumor necrosis and loss of immunoreactivity for markers commonly expressed by endometrial stromal cells (CD 10, ER, and PR) than the sarcomatous component of typical adenosarcomas. Adenosarcomas with sarcomatous overgrowth have been found to be more aggressive than the typical adenosarcomas, with recurrences, metastasis, and tumor related deaths occurring at rates similar to leiomyosarcoma or carcinosarcoma.

The immunophenotype of adenosarcomas closely parallels that of endometrial stromal neoplasms when there is no sarcomatous overgrowth. The mesenchymal component typically expresses ER, PR, androgen receptors, CD10, and WT1, while few tumors also express smooth muscle actin and pan-cytokeratins [18]. Cases demonstrating stromal overgrowth generally lose strong and diffuse ER, PR, CD10, and WT1 expression. Tumors containing heterologous elements exhibit an immunophenotype that is similar to eutopic tumors; therefore, the mesenchymal component of an adenosarcoma with rhabdomyoblastic differentiation would be expected to express desmin, myogenin, and myoD1. As with carcinosarcomas, recent work suggests that the presence of rhabdomyoblastic differentiation portends a poor prognosis. The proliferative index, estimated with a Ki-67 immunostain, increases with mitotic rate and the presence of sarcomatous stromal overgrowth.

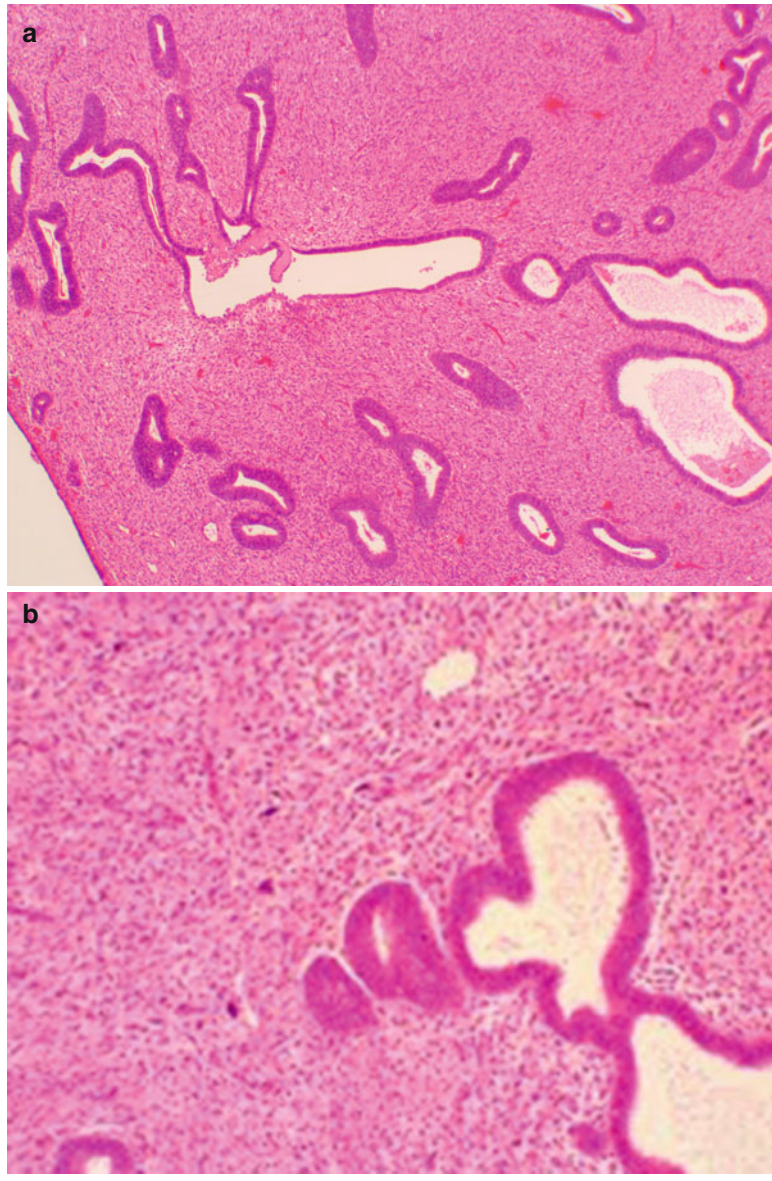


Fig. 11.4 (**a**) Adenosarcoma with slit-like glands in sarcomatous stroma. (**b**) Adenosarcoma with sarcomatous stroma under higher magnification. (**c**) Adenosarcoma with the sarcomatous stroma showing pleomorphic cells

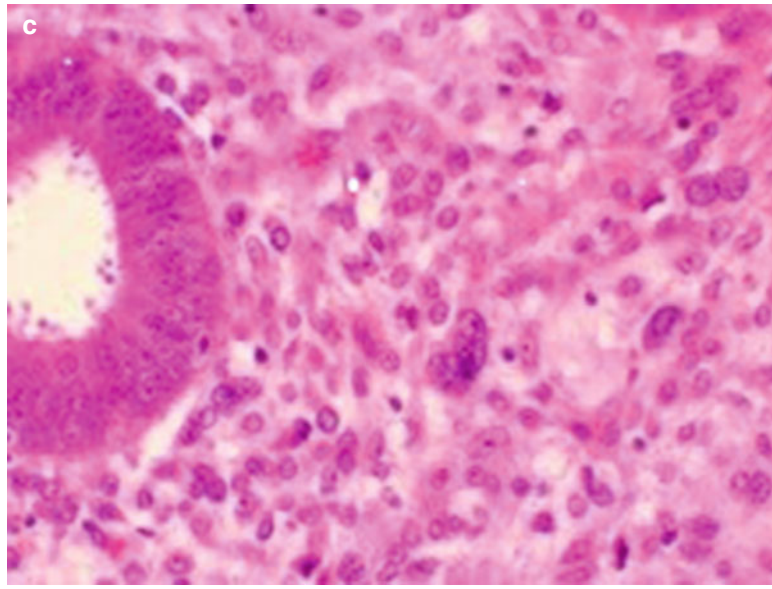


Fig. 11.4 (continued)

Carcinosarcoma

Carcinosarcomas, synonymous with malignant mixed Mullerian tumor and malignant mixed mesodermal tumor (MMMT), were traditionally considered as the most common subtype of uterine sarcomas, accounting for 40–50 % of uterine sarcomas. These tumors are now considered to represent metaplastic carcinomas – a special variant of endometrial adenocarcinoma. However, the tumor is described here in some detail because carcinosarcomas with a predominance of sarcomatous elements are often misdiagnosed as one of the rare heterologous sarcomas. The term carcinosarcoma is now used for all primary uterine neoplasms containing malignant elements of both epithelial and stromal light microscopic appearance, regardless of whether malignant heterologous elements are present.

It is a biphasic neoplasm composed of an admixture of epithelial and mesenchymal elements, both of which are malignant. Though these tumors have traditionally been considered a subtype of uterine sarcomas, mounting clinical, histological, immunologic, and molecular data strongly support the concept that these tumors represent metaplastic carcinomas, hence they are now considered a special variant of endometrial adenocarcinoma [19]. However, though 80–90 % of CSs are monoclonal, 10–20 % of the tumors are biclonal and represent true collision tumors.

Carcinosarcomas typically occur in postmenopausal women who present with abnormal vaginal bleeding, uterine enlargement, and abdominopelvic pain. The serum level of CA125 is elevated in most cases. Rarely these tumors are seen in women less than 40 years. Extrauterine spread (stages III-IV) is present at presentation in up to one-third of cases. Up to 37 % of patients with CSs have a history of pelvic irradiation. These tumors tend to occur in younger women, often contain heterologous elements, and are found at advanced stage.

Gross Features

CSs are large and bulky broad-based, polypoid tumors that distend the endometrial cavity and invade the myometrium. The tumors may protrude through the external os. Cut surfaces are fleshy with hemorrhagic and necrotic areas.

Gritty or hard areas may be present, corresponding to bone or cartilage. Occasional tumors may arise within an endometrial polyp.

Microscopic Features

The carcinomatous component of CS is typically a high-grade adenocarcinoma with endometrioid or serous differentiation and rarely clear cell or other less common carcinomas. The sarcomatous component is also usually high-grade with homologous or heterologous tissues. Homologous sarcoma is usually composed of nondescript spindle, oval, or round cells with significant nuclear atypia and mitotic activity resembling sarcomas derived from endometrial stroma, fibrosarcoma, or rarely leiomyosarcoma (Fig. 11.5a, b). Heterologous sarcomatous

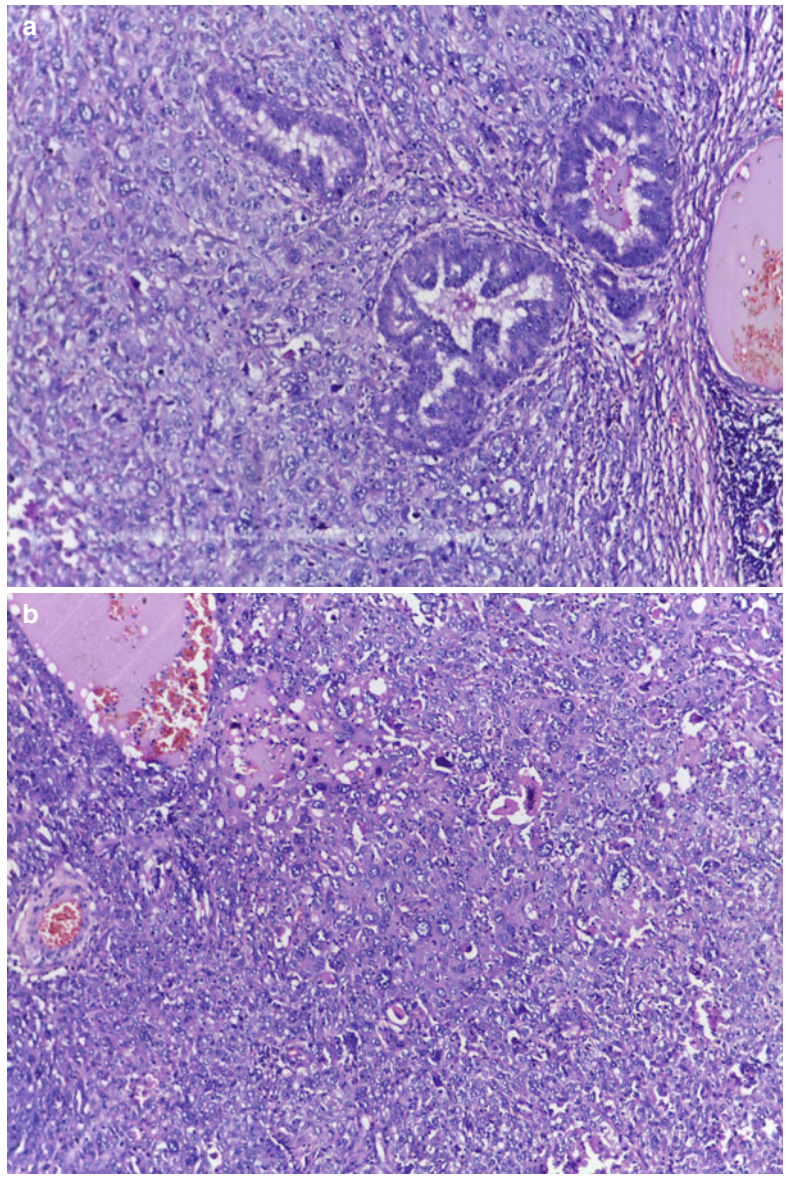


Fig. 11.5 (**a**) Carcinosarcoma with malignant epithelial and sarcomatous stromal elements. (**b**) Sarcomatous stroma of carcinosarcoma. (**c**) Carcinosarcoma with malignant epithelial and heterologous stromal component. (**d**) Carcinosarcoma with chondrosarcomatous areas

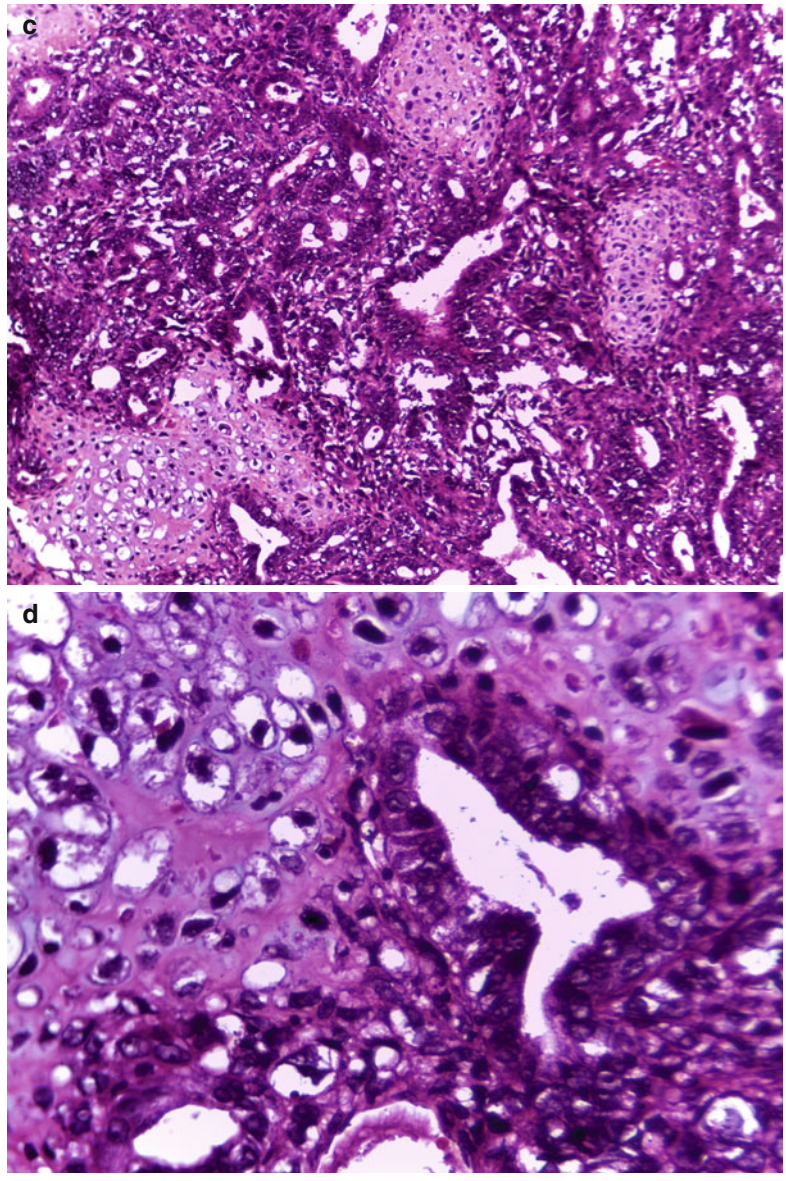


Fig. 11.5 (continued)

elements are usually rhabdomyosarcoma**,** chondrosarcoma (Fig. 11.5c, d), osteosarcoma, and liposarcoma**.**

Carcinosarcomas are aggressive neoplasms that as a group have a prognosis that is worse than both high-grade endometrial adenocarcinoma and the high risk subtypes of serous and clear cell carcinoma, and tumor stage is the most powerful prognostic predictor. The potential prognostic significance of heterologous elements is controversial [20].

Other Rare Sarcomas

Perivascular epithelioid cell tumors ("PEComa") and uterine tumor resembling ovarian sex cord tumor (UTROSCT) (Fig. 11.6a) are rare mesenchymal tumors of the uterus with distinct morphological and immunohistochemical features. These tumors are considered to be neoplasms of low malignant potential.

Sarcomas other than those described above can arise in the uterus from tissues that are not

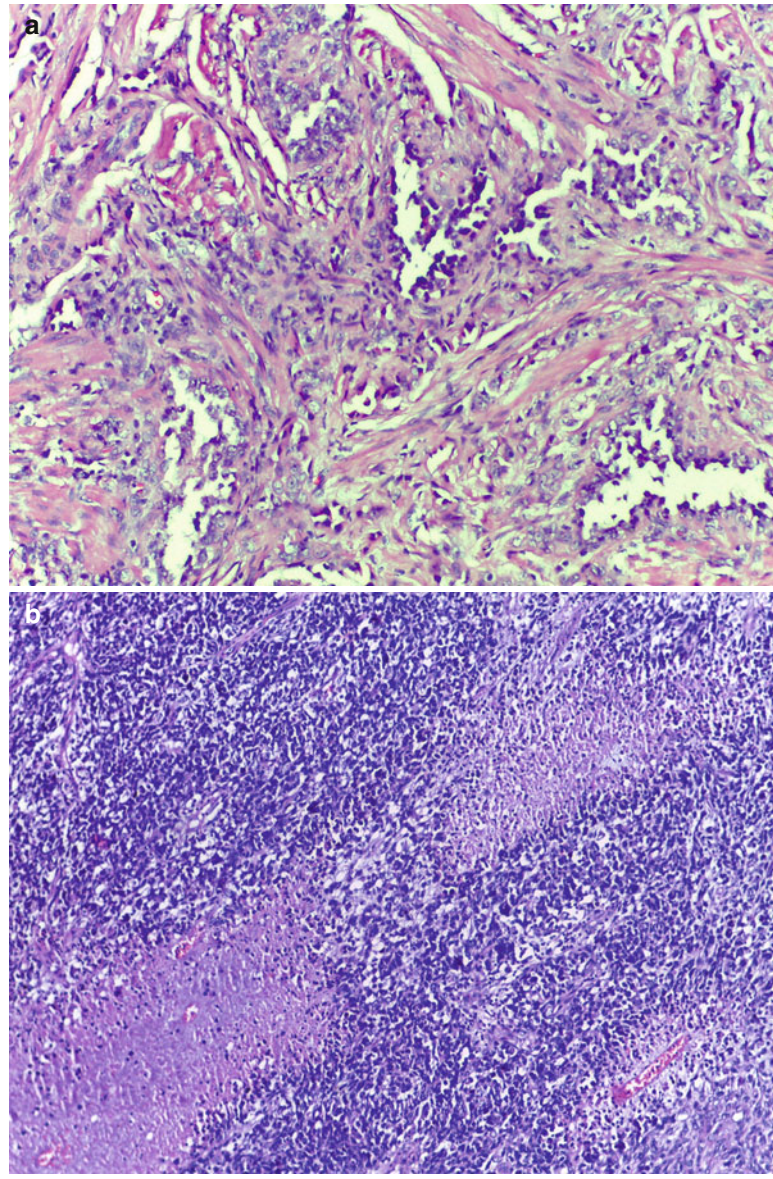


Fig. 11.6 (**a**) Uterine tumor resembling ovarian sex cord tumor. (**b**) Embryonal rhabdomyosarcoma

endometrial stromal or smooth muscle in type. These tumors are rare and are similar to their counterparts arising in more usual sites. They include rhabdomyosarcoma-embryonal in young females (Fig. 11.6b) and pleomorphic in the middle aged and elderly. Liposarcoma, chondrosarcoma, osteosarcoma, malignant peripheral nerve sheath tumor, angiosarcoma, malignant fibrous histiocytoma, malignant mesenchymoma, alveolar soft part sarcoma, GIST, rhabdoid sarcoma, Ewing sarcoma/PNET, and tumors with neuroectodermal differentiation but lacking the EWSRI gene rearrangement [21–23]. In general these tumors are all bulky neoplasms and frequently high stage at presentation. Immunohistochemical studies may assist in establishing a definitive diagnosis of these tumors. However before making a diagnosis of these rare sarcomas, particularly if the tumor is very pleomorphic and includes heterologous elements, the more likely possibility of carcinosarcoma with predominance of the sarcoma-like component should be ruled out with thorough sampling [24].

Conclusion

Uterine sarcomas are a heterogeneous group of rare tumors with aggressive clinical behavior and poor prognosis. The recent changes in the classification and staging of these tumors have helped in understanding the different behavioral patterns of these tumors. Accurate typing of uterine sarcoma is vital since the behavior, management, and patient outcome differ markedly between the different tumor types. Immunohistochemistry and molecular studies can be of use in certain situations in the evaluation of uterine sarcomas. The results of immunohistochemistry should always be interpreted in conjunction with the clinical features and gross and microscopic findings. More knowledge about the genetic aberrations and genomic rearrangements responsible for uterine sarcoma genesis may help in the development of more effective therapies.

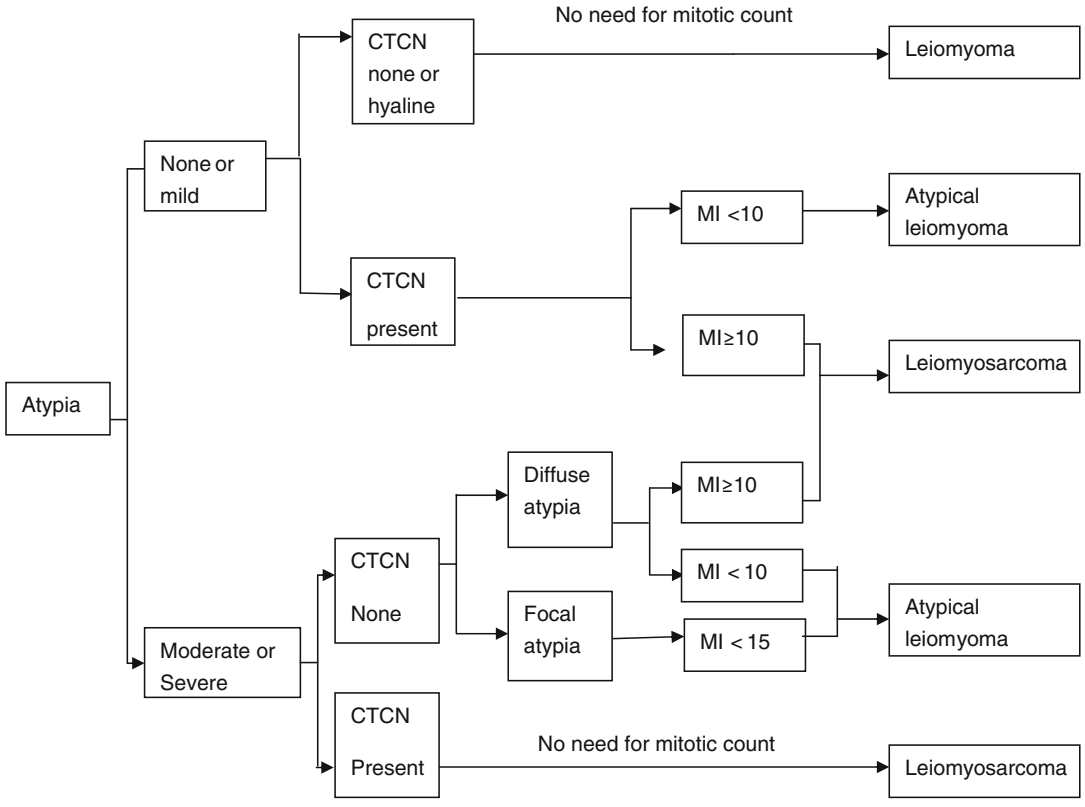
Key Points

1. 3–5 % of malignant uterine tumors contain a malignant mesenchymal component. With the updated classification (excluding CS) LMS accounts for 60 % of the tumors, ESS 30 %, UUS –5 %, and AS and other uterine sarcomas 5 % which includes malignant PEComa, UTROSCT, rhabdomyosarcoma, PNET, angiosarcoma, osteosarcoma, chondrosarcoma, liposarcoma, alveolar soft part sarcoma, malignant rhabdoid tumor, and other very rare tumors.
2. The historic classification of uterine sarcomas which categorized endometrial stromal sarcomas into the low and high-grade ESS based on the mitotic activity had been replaced by ESS and UUS in the (2003) WHO classification of tumours of the uterine corpus. However, recent molecular and morphological data have validated the re-introduction of high-grade endometrial stromal sarcoma, for a specific subset of uterine sarcomas. The latest (2014) WHO classification includes low-grade ESS, high-grade ESS, UUS and UTROSCT in the endometrial stromal group of tumors.
3. Carcinosarcomas are now considered metaplastic carcinomas and the term is now used for all primary uterine neoplasms containing malignant elements of both epithelial and stromal light microscopic appearance, regardless of whether malignant heterologous elements are present.
4. The 2009 FIGO staging system has developed specific staging systems for LMS and ESS and for AS. Carcinosarcoma continues to be staged as an endometrial carcinoma.
5. Leiomyosarcoma, undifferentiated uterine sarcoma, and the heterologous sarcomas are, in general, highly aggressive tumors with a high propensity for extrauterine spread and systemic metastasis while the low-grade endometrial stromal tumors are indolent neoplasms which are compatible with long-term survival despite the tendency for late recurrences or metastatic spread.
6. Adenosarcomas are mixed tumors of low malignant potential containing a benign epithelial and a malignant stromal component, usually of low grade. They are usually polypoid neoplasms that project into the uterine cavity and have a favorable prognosis unless associated with sarcomatous overgrowth or deep myometrial invasion.
7. It is almost impossible to distinguish low-grade ESS from a stromal nodule, a nonneoplastic stromal proliferation or a highly cellular leiomyoma in an endometrial biopsy or a curettage sample since the distinction is mainly based on the appearance of the stromal-myometrial interface.
8. Leiomyosarcoma is only infrequently diagnosed on endometrial samplings.

9. Disease stage is the most important prognostic factor for all types of US. However, the prognosis of stage I LMS is also significantly related to tumor size and mitotic index (MI), and that of stage I ESS is related to MI and tumor cell necrosis (TCN). In adenosarcoma, TCN is the only significant histopathological prognostic factor [25].
10. Molecular studies are proving to be of value in the diagnosis of uterine sarcomas, and these are becoming routinely available in specialist centers. Many, but not all, of the techniques can be performed on formalin-fixed paraffin-processed tissue. A recurrent t (7; 17) (p15;q21) translocation resulting in a JAZF1-JJAZ1 gene fusion has been demonstrated in over 60 % of endometrial stromal tumors, including its variants. A group of high-grade endometrial stromal sarcomas harbors the YWHAE-FAM22 genetic fusion as a result of t(10;17)(q22;p13). Molecular studies may also be useful to confirm the diagnosis in problematic cases. Other sarcomas that occasionally occur in the uterus, like the alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and neoplasms in the Ewing family of tumors demonstrate consistent molecular abnormalities.

Appendix

The histological diagnosis of leiomyosarcoma



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