Mesenchymal Tumors of the Uterus

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Contents

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This chapter deals with neoplasms of the uterus in which there is mesenchymal differentiation. Purely mesenchymal tumors, such as those derived from smooth muscle and endometrial stroma, are considered, as are some benign and malignant neoplasms containing mixtures of epithelium and connective tissue. The categories used here are slightly modified from the comprehensive classification of mesenchymal neoplasms of the uterus developed by the World Health Organization (WHO) (Kurman et al. 2014), shown in Table 1.

Proper pathologic study of a mesenchymal tumor of the uterus requires careful gross examination and adequate sectioning. The tumor should be examined thoroughly, and one block of tissue should be taken for each centimeter of tumor diameter, except from grossly typical leiomyomas; even the latter may have to be examined extensively if the microscopic appearance is unusual. Three major goals of prosecting potentially malignant mesenchymal tumors are to determine the type of tumor margin (expansile or infiltrating), to evaluate the depth of myometrial invasion, and to determine whether the tumor involves the serosa or extends beyond the uterus. Tissue samples should be taken with these requirements in mind.

The most common uterine tumors are leiomyomas, while other types of benign and malignant mesenchymal tumors are uncommon. Malignant mesenchymal tumors comprise less than 3% of uterine malignancies. Tumor stage is the single most important prognostic factor. In the past, uterine sarcomas were staged using a system developed for endometrial carcinoma. This has not proven entirely satisfactory, and a new staging system has been developed for uterine sarcomas (Table 2) (Prat 2009). The new staging system has two compartments, one for leiomyosarcoma and endometrial stromal sarcoma and another for adenosarcoma. Carcinosarcoma, or mixed mullerian tumor (see ▶ Chap. 9, "Endometrial Carcinoma"), is a mixed epithelial-mesenchymal neoplasm in which both elements are malignant; it has much in common with endometrial carcinoma and is staged using the endometrial carcinoma staging system. The staging system for uterine tumors is a surgical-pathologic one, so pathologists must be familiar with the criteria for staging and make certain to provide all information necessary for staging in their surgical pathology reports.

Smooth Muscle Tumors

Smooth muscle neoplasms of the uterus are extremely common, and most are leiomyomas. These tumors may be incidental in uteri removed for other reasons, but they are also frequently responsible for a variety of common gynecologic and obstetric difficulties. Histologically, all but a small minority of leiomyomas are easily identified as benign and having a smooth muscle phenotype. A small percentage of uterine smooth muscle neoplasms are leiomyosarcomas, which according to modern diagnostic criteria are highly malignant neoplasms. Most leiomyosarcomas are easily recognized as malignant and showing smooth muscle differentiation. A small number of uterine smooth muscle proliferations pose diagnostic challenges for a variety of reasons involving either unclear phenotype or anticipated clinical behavior (benign or malignant or something in between).

This discussion of smooth muscle neoplasms first presents a general approach to their evaluation, detailing the features that need to be assessed: type of differentiation, degree of cellularity, mitotic index, presence and degree of cytologic atypia, and presence of necrosis and its pattern. The second section deals with the

Table 1 Classification of mesenchymal and mixed tumors of the uterus, modified from WHO 2014

Smooth muscle tumors
Leiomyoma
Mitotically active leiomyoma
Cellular leiomyoma
Apoplectic leiomyoma
Fumarate hydratase-deficient leiomyoma
Leiomyoma with bizarre nuclei
Epithelioid leiomyoma
Myxoid leiomyoma
Vascular leiomyoma
Leiomyoma with other elements
Lipoleiomyoma
Leiomyoma with hematopoietic cells
Diffuse leiomyomatosis
Dissecting leiomyoma
Smooth muscle tumor of uncertain/low malignant potential
Leiomyosarcoma
Conventional (spindle) leiomyosarcoma
Epithelioid leiomyosarcoma
Myxoid leiomyosarcoma
Other smooth muscle tumors
Benign Metastasizing leiomyoma
Intravenous leiomyomatosis
Disseminated peritoneal leiomyomatosis
Perivascular Epithelioid Cell Tumor and related lesions (angiomyolipoma and lymphangioleiomyomatosis)
Endometrial stromal tumors
Endometrial stromal nodule
Endometrial stromal sarcoma (low grade)
Endometrial stromal sarcoma (high grade)
Undifferentiated endometrial sarcoma
Mixed epithelial-mesenchymal tumors
Benign
Adenofibroma
Adenomyoma
Malignant
Adenosarcoma (homologous or heterologous)
Uterine tumor resembling ovarian sex cord tumor (UTROSCT)
Inflammatory myofibroblastic tumor (IMT)
Heterologous and homologous sarcomas other than leiomyosarcoma and endometrial stromal sarcoma
Rhabdomyosarcoma
Alveolar soft part sarcoma
Primitive neuroectodermal tumor (PNET)
Miscellaneous mesenchymal tumors
Adenomatoid tumor
Vascular tumors
Lymphoma

Table 2 Staging for uterine sarcomas

(1) Leiomyosarcoma and endometrial stromal sarcoma (ESS)		
Stage		Definition
I		Tumor limited to uterus
	IA	<5 cm
	IB	>5 cm
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
(2) Mullerian adenosarcoma[a]		
Stage		Definition
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
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

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

epidemiology, pathology, molecular biology, cytogenetics, clinical course, and treatment of each of the named smooth muscle entities.

Evaluation of Smooth Muscle Neoplasms

The most effective way to distinguish clinically benign from clinically malignant uterine smooth muscle neoplasms is through the use of

multivariate criteria, that is, criteria that consider several microscopic features as an ensemble (Bell et al. 1994; Longacre et al. 1997). These features include differentiated cell type within the smooth muscle group, presence and type of tumor necrosis, degree of cytologic atypia, mitotic index, and the relationship of the neoplasm to surrounding normal structures, including extrauterine sites.

Differentiated Cell Type

The term usual smooth muscle differentiation denotes a pattern of differentiation recapitulating that of the constituent cells of the normal myometrium. Usual smooth muscle cells are elongated; possess distinct cell membranes; have readily apparent eosinophilic, sometimes fibrillar cytoplasm; and grow in a fascicular arrangement. Since malignant spindle cell tumors other than leiomyosarcoma arise in the uterus, desmin and caldesmon immunohistochemical stains are useful for ascertaining smooth muscle differentiation when a tumor's appearance departs from the above description. These non-leiomyosarcoma spindle cell tumors include spindle cell variants of endometrial stromal sarcoma (Lewis et al. 2017; Oliva et al. 1999; Yilmaz et al. 2002), the sarcomatous component of adenosarcoma or carcinosarcoma, undifferentiated sarcoma (Kurihara et al. 2008), gastrointestinal stromal tumor, heterologous sarcoma (Fadare 2011), malignant solitary fibrous tumor (Baldi et al. 2013; Yang et al. 2017), and the extremely rare fibrosarcoma (Chiang et al. 2018).

Epithelioid smooth muscle cells are round or polygonal and have eosinophilic to colorless cytoplasm. They may have perinuclear cytoplasmic vacuoles or there may be a perinuclear rim of eosinophilic cytoplasm while the rest of the cytoplasm is clear. When the cytoplasm is completely clear, the label "clear cell" is used. To distinguish perivascular epithelioid cell tumor (PEComa) from other myometrial epithelioid tumors, HMB45 and Melan-A stains are helpful (see section "PEComa and Related Lesions" at the end of this chapter). Other neoplasms in this category include metastatic (or locally invasive) carcinoma (cytokeratin positive), metastatic melanoma (S-100 positive), placental site and epithelioid trophoblastic tumors (GATA-3 positive), and alveolar soft part sarcoma (ASPS) (HMB-45 negative with *Xp11* translocation). Some endometrial stromal neoplasms may have an epithelioid appearance (Lee et al. 2012b).

Myxoid smooth muscle proliferations feature widely spaced stellate cells with inapparent cytoplasm embedded in a myxoid matrix. Malignant myxoid smooth muscle neoplasms exhibit varying degrees of cytologic atypia and often have an appearance reminiscent of myxofibrosarcoma (myxoid malignant fibrous histiocytoma or myxofibrosarcoma) of the soft tissues. Tumors in this category include hydropic leiomyoma (edema fluid, not stromal mucin) (Clement et al. 1992), the vanishingly rare myxoid leiomyoma, myxoid change (Pugh et al. 2012), inflammatory myofibroblastic tumor (IMT) (*ALK*-rearranged) (Bennett et al. 2017a; Parra-Herran et al. 2015; Rabban et al. 2005), and fibromyxoid variants of endometrial stromal sarcoma (Lewis et al. 2017; Oliva et al. 1999; Yilmaz et al. 2002).

Less common types of differentiation, such as fat and skeletal muscle, are discussed later (see section "Leiomyomas with Other Elements").

Patterns of Necrosis

The presence or absence and type of necrosis are powerful predictors of clinical behavior (Bell et al. 1994). Two patterns of necrosis in uterine smooth muscle tumors are diagnostically important: coagulative tumor cell necrosis and hyalinizing (or "infarction-type") necrosis (Bell et al. 1994).

Recognizing coagulative tumor cell necrosis is crucial because it is a key distinguishing feature of clinically malignant smooth muscle neoplasms. Coagulative tumor cell necrosis features an abrupt transition between necrotic and preserved cells (Fig. 1), where necrotic cells retain nuclear hematoxyphilia, and usually without associated inflammation or hemorrhage. The characteristic low-power microscopic pattern is one of blood vessels cuffed by viable cells surrounded by a sea of necrotic tumor (Bell et al. 1994; Clement 2000). In contrast, hyalinizing necrosis,

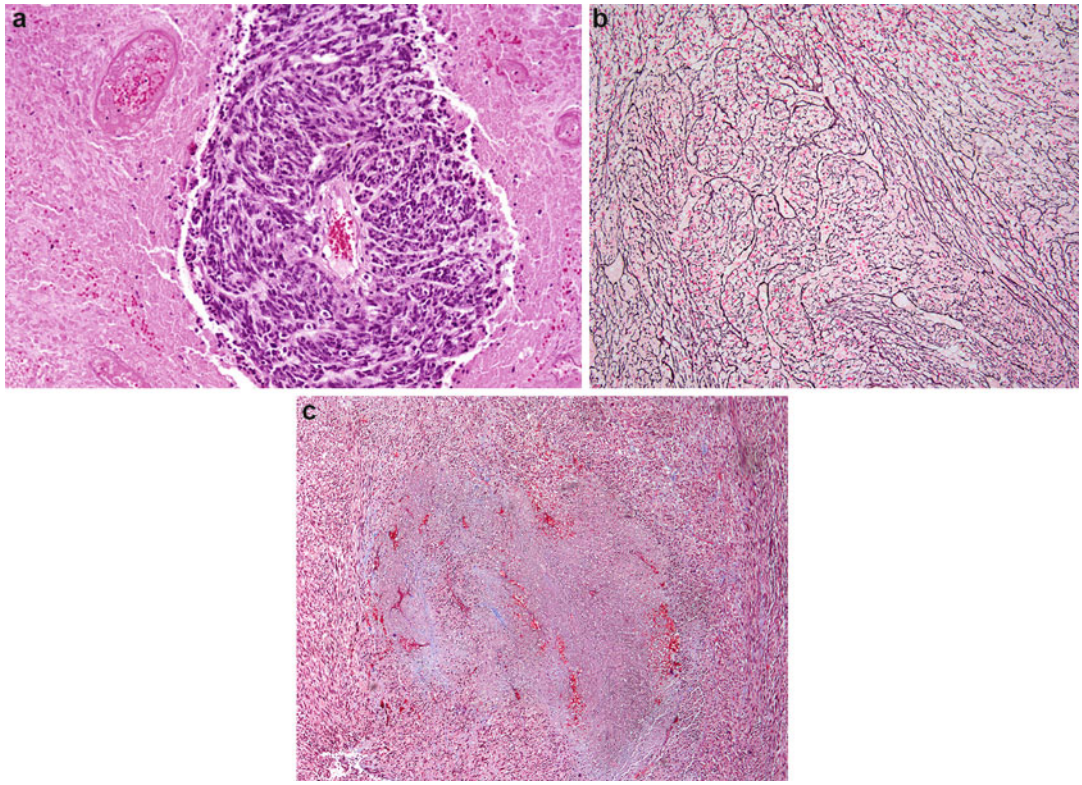

Fig. 1 **Coagulative tumor cell necrosis.** (**a**) Viable cells are present only around the blood vessel. Ghostlike outlines of necrotic atypical tumor cells can still be discerned in the surrounding tissue. (**b**) Reticulin network is preserved. (**c**) Collagen deposition is not obvious (trichrome stain)

associated with damage following ischemia, has a distinctly zonal pattern with central necrosis, a more peripheral zone of granulation tissue, and, at the periphery, a variable amount of hyaline eosinophilic collagen interposed between the central degenerated region and peripheral preserved smooth muscle cells (Fig. 2). Hemorrhage is frequently present. When shadow cells or nuclei are discernible in the necrosis, there is little hyperchromasia or nuclear pleomorphism.

One challenge in discerning coagulative tumor cell necrosis is its similarity to acute infarction (Fig. 3); both involve juxtaposition of preserved tumor adjacent to necrotic tumor. Coagulative tumor cell necrosis may be distinguished from acute ischemic necrosis by (1) the presence of hyperchromasia and nuclear pleomorphism in the "shadow cells" of the necrotic tumor and (2) (in the absence of these nuclear features) the absence of ongoing ischemia elsewhere in the problematic smooth muscle neoplasm. The presence of viable, benign-appearing smooth muscle at the periphery of the devitalized tissue and hemorrhage argues strongly in favor of an early infarct, as does the absence of viable vessels within the infarct and sarcoma ghost cells.

Unfortunately, there is a considerable degree of interobserver variation in the distinction between coagulative tumor cell necrosis and hyalinizing (postischemic) necrosis (Lim et al. 2013). Trichrome preparations are useful in detecting patchy foci of healed ischemic damage. A recent study showed that a combination of reticulin and trichrome histochemical stains and a Ki-67 immunostain helps discriminate these types of necrosis, although with imperfect accuracy. Most infarcts stain blue with trichrome, show reticulin loss, and, in some cases, display a rim of proliferation around the infarct that differs from more distant parts of the tumor. On the other hand, coagulative tumor cell necrosis usually

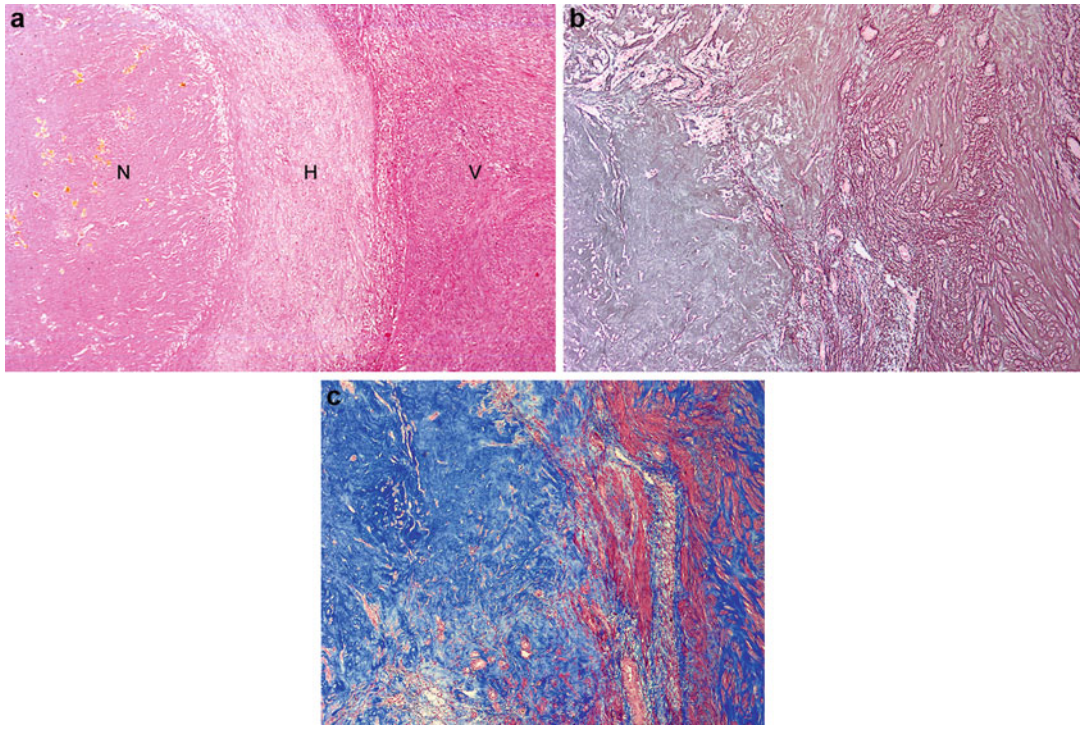

Fig. 2 Hyalinized necrosis. (**a**) An area of bland necrosis (N) is separated from viable spindle-shaped tumor cells (V) by a zone of hyalinized collagen (H). (**b**) Reticulin network is lost, in contrast to coagulative tumor cell necrosis (Fig. 1b). (**c**) Hyalinizing necrosis. Collagen deposition is present (trichrome stain), unlike coagulative tumor cell necrosis (Fig. 1c)

but not always retains reticulin, but not trichrome staining, and exhibits less proliferation adjacent to the necrosis compared to viable portions of the tumor (Yang and Mutter 2015).

Another pattern of necrosis that may be seen in ulcerated submucous leiomyomas features acute inflammatory cells and an associated zonal reparative process.

Cytologic Atypia

Several studies have demonstrated a relationship between cytologic atypia and clinical behavior in uterine smooth muscle neoplasms (Bell et al. 1994). The problem, as always, is defining "significant atypia" in a way that is reproducible and can be communicated to others. Bell et al. found that a two-tiered scheme of absent to mild atypia versus diffusely distributed moderate to severe atypia is reasonably reproducible, where moderate to severe atypia is defined as nuclear hyperchromatism and pleomorphism that is obvious at scanning power (Fig. 4) (Bell et al. 1994). Neoplasms with this level of atypia often display enlarged and sometimes abnormal mitotic figures. Most commonly, moderate to severe atypia is present diffusely throughout the neoplasm, as in pleomorphic undifferentiated sarcoma (also termed malignant fibrous histiocytomas of the soft tissue), but it can, occasionally, be present only focally. In contrast, absent or mild atypia features uniform cells with no more than mild nuclear pleomorphism (Fig. 5), with fine to granular chromatin. The nuclei may be enlarged in comparison to those of the cells comprising the surrounding myometrium, but the enlargement is uniform throughout the tumor. More than one or two enlarged abnormal mitotic figures are sufficient to classify a tumor's atypia as moderate to severe.

Diffuse severe atypia may also manifest as uniformly enlarged, hyperchromatic cells (Fig. 6) that

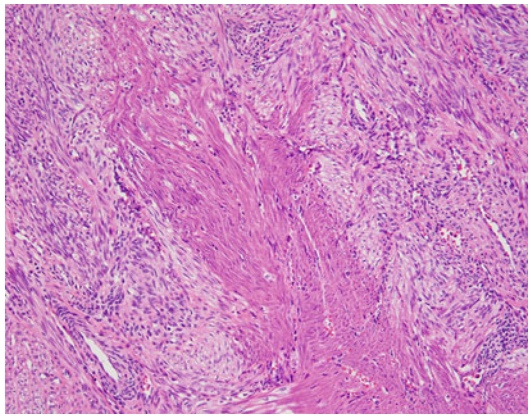

Fig. 3 Early infarct, mimicking coagulative tumor cell necrosis. Despite an abrupt transition from viable to necrotic tumor, the background lacks atypia and the necrotic focus does not contain hyperchromatic, atypical ghost cells

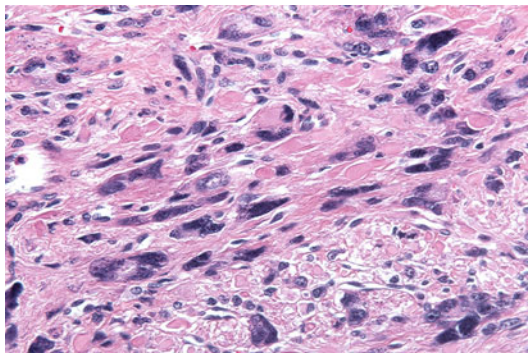

Fig. 4 Severe pleomorphic atypia. Nuclear pleomorphism against a background of diffuse severe atypia of spindled cells

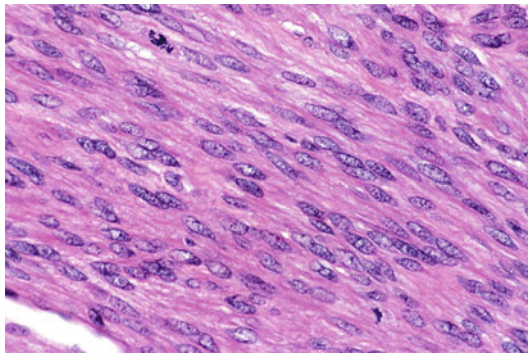

Fig. 5 Diffuse mild atypia. Uniform mild atypia characterizes this infiltrating smooth muscle neoplasm

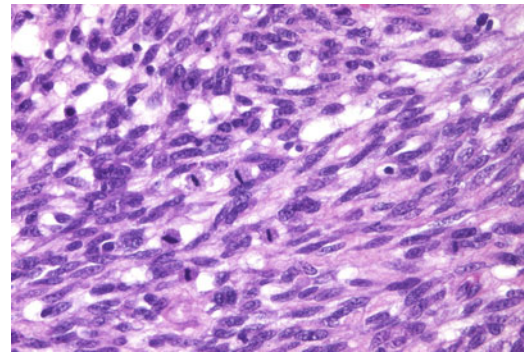

Fig. 6 Severe uniform atypia. Relatively uniform malignant cells exhibiting nuclear hyperchromasia and a high mitotic index

are difficult to discern as "atypical" on scanning magnification because nuclei do not appear pleomorphic; this pattern is analogous to that seen, for example, in monophasic synovial sarcoma of the soft tissues. Despite the absence of pleomorphism, this type of atypia must still be recognized; one key is to compare the constituent cells of the tumor to the surrounding normal myocytes to look for nucleomegaly and hyperchromasia of the neoplastic cells. A helpful adjunct in diagnosing leiomyosarcomas with this type of uniform severe atypia is the variably associated finding of infiltration of the surrounding myometrium.

Mitotic Index

Mitotic index is expressed in terms of the number of definite mitotic figures per 10 high-power fields (Hilsenbeck and Allred 1992; van Diest et al. 1992). Whether intensive mitosis counting is required depends on whether significant cytological atypia or tumor cell necrosis is present. In the absence of these two features the precise mitotic index is of little importance below 20 mitotic figures per 10 high-power fields (MF/10 HPF).

The mitotic index is determined by searching the slide at low magnification for the most mitotically active area, then counting the mitotic figures within that area at high magnification in five sets of 10 randomly chosen contiguous fields. Care must be taken not to count lymphocytes, karyorrhectic debris, precipitated hematoxylin, or mast cells as mitotic figures. Most reliable are mitotic figures in metaphase,

anaphase, or telophase. The reproducibility of mitotic counts may depend on consistent counting techniques (O'Leary and Steffes 1996) or on accurately defining a mitotic figure. Phosphohistone H3 staining can be used as an adjunct to traditional mitotic counting (Chow et al. 2017).

Relationship to Surrounding Normal Structures and Anatomic Distribution

Another indicator of a smooth muscle neoplasm's aggressiveness is its relationship to the surrounding myometrium and uterine vessels and whether it extends beyond the uterus. Infiltrative margins, intravascular growth, and extrauterine spread, although commonly encountered in uterine malignancies, are not, when seen as isolated findings, diagnostic of sarcoma. Some relatively rare benign or clinically low-grade smooth muscle proliferations mimic leiomyosarcoma by virtue of their relationship to normal uterine structures or their extrauterine extension.

Leiomyoma

Leiomyomas are the most common uterine neoplasms (Payson et al. 2006; Vollenhoven 1998). They are noted clinically in 20–30% of women over 30 years of age, and are found in as many as 75% of uteri upon systematic searching (Baird et al. 2003; Cramer and Patel 1990; Payson et al. 2006). Leiomyomas are usually detected in middle-aged women and are uncommon in women less than 30 years of age; however, the youngest patient on record was 13 years old. Some leiomyomas apparently shrink after menopause, but their frequency does not decrease. Leiomyomas are more common in African American women than in white women (Kjerulff et al. 1996).

The growth of leiomyomas is affected by the hormonal milieu (Andersen 1998; Marsh and Bulun 2006; Rackow and Arici 2006; Sozen and Arici 2006), as they contain estrogen receptors (ER) and progesterone receptors (PR) (Viville et al. 1997). Leiomyomas may grow larger during estrogen therapy, and most become smaller when the patient is treated with a gonadotropin-releasing hormone (GnRH) agonist (Adamson 1992; Regidor et al. 1995; Shaw 1998; Stovall et al. 1991; Upadhyaya et al. 1990). Progestins, progesterone, hormone replacement therapy, clomiphene use, and pregnancy occasionally are associated with rapid leiomyoma growth and sometimes produce hemorrhagic degeneration (Sener et al. 1996).

Clinical Features

The clinical presentation of leiomyomas depends on their size and location (Bukulmez and Doody 2006). Leiomyomas cause many signs and symptoms, the most common of which are pain, a sensation of pressure, and abnormal uterine bleeding. Even small leiomyomas, when submucosal, can cause bleeding due to compression of the overlying endometrium and compromise of its vascular supply. In some instances, infertility is attributed to the presence of leiomyomas. Large tumors can be detected during pelvic examination because they cause uterine enlargement or an irregular uterine contour. Some leiomyomas are pedunculated and protrude through the cervical os. On rare occasions, subserosal pedunculated leiomyomas undergo torsion, infarction, and separation from the uterus. Secondary infection of leiomyomas can result in fever, leukocytosis, and an elevated sedimentation rate. Among the complications of pregnancy ascribed to leiomyomas are spontaneous abortion, premature rupture of membranes, dystocia, inversion of the uterus, and postpartum hemorrhage.

Gross Findings

Despite the variety of histologic subtypes of leiomyoma, many are grossly similar. Multiple leiomyomas are present in two-thirds of women with these neoplasms (Cramer and Patel 1990). Leiomyomas are spherical and firm and bulge above the surrounding myometrium. The cut surfaces are white to tan, with a whorled trabecular pattern (Fig. 7). Leiomyomas can be located

anywhere in the myometrium but are most commonly intramural. Submucosal leiomyomas compress the overlying endometrium and bulge into the endometrial cavity as they enlarge. Very rarely, some become attached to another pelvic structure (parasitic leiomyoma). The appearance of a leiomyoma is commonly altered by degenerative changes, such as hemorrhage, appearing as dark red areas, and necrosis, which can be recognized as sharply demarcated yellow areas. These features are more common in large leiomyomas and those of women who are pregnant or undergoing high-dose progestin therapy. Submucosal leiomyomas are frequently ulcerated and hemorrhagic. The hemorrhagic infarction damages smooth muscle, which is eventually replaced by firm white or translucent collagenous tissue. Cystic degeneration also occurs, and some leiomyomas become extensively calcified. The precise locations of leiomyomas may be determined by transvaginal ultrasound, which in complex cases is complemented by magnetic resonance imaging (Dueholm et al. 2002; Vitiello and McCarthy 2006).

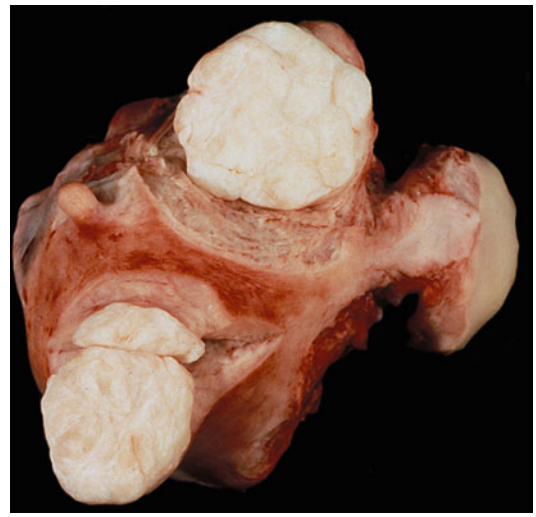

Fig. 7 Enlarged uterus containing multiple leiomyomas. The leiomyomas have a whorled white-tan cut surface that bulges above the surrounding myometrium

Microscopic Findings

Typical leiomyomas are composed of whorled, anastomosing fascicles of uniform fusiform smooth muscle cells. The spindle-shaped cells have indistinct borders and abundant fibrillar eosinophilic cytoplasm (Fig. 8). Nuclei are elongated with blunt or tapered ends and have finely dispersed chromatin and small nucleoli. Mitotic figures usually are infrequent. Most leiomyomas are more cellular than the surrounding myometrium; those that are not are identified by their nodular circumscription and by the disorderly arrangement of the smooth muscle fascicles within them, which are out of alignment with the surrounding myometrium.

The degenerative changes mentioned above are also apparent microscopically. Hyaline fibrosis is present in more than 60%, particularly in postmenopausal women (Cramer et al. 1996). Edema is present in about 50% of leiomyomas, and, on occasion, marked hydropic change can

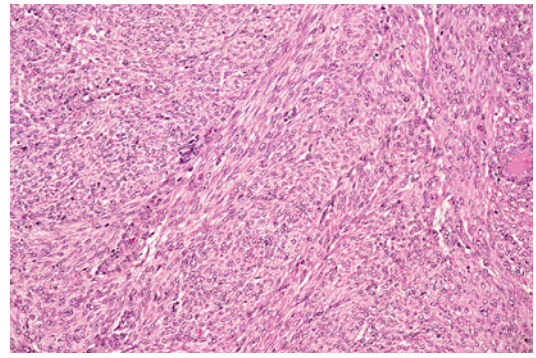

Fig. 8 Typical leiomyoma. The spindle-shaped tumor cells have cytologically bland, relatively uniform nuclei with fine chromatin and small nucleoli. The cytoplasm is abundant, eosinophilic, and fibrillar

mimic the appearance of a myxoid smooth muscle tumor or produce a pattern that can be confused with intravenous leiomyomatosis (IVL) (Clement et al. 1992; Coad et al. 1997). About 10% of leiomyomas contain significant areas of hemorrhage, which tend to be zonal and sharply demarcated, and cystic degeneration and microcalcification each occurs in about 4%. In addition to hemorrhage, edema, myxoid change, hypercellular foci, and cellular hypertrophy are also particularly frequent in the leiomyomas of women who are pregnant or taking progestins

(see following, section "Apoplectic Leiomyoma/Hemorrhagic Cellular Leiomyoma") (Bennett et al. 2016). Progestational agents are associated with a slight increase in mitotic activity but not to the level observed in a leiomyosarcoma.

The margins of most leiomyomas are microscopically circumscribed, but some benign tumors interdigitate with the surrounding myometrium, occasionally extensively (see following, section "Dissecting Leiomyomas"). Submucous leiomyomas, particularly if they protrude into the endometrial cavity, may display extensive necrosis, often with acute inflammatory cells, unlike the necrosis common in leiomyosarcoma. The necrosis in these tumors is also distinguishable from that in malignant tumors by the inconspicuousness or absence of cell outlines. Not infrequently, areas of necrosis are accompanied by adjacent regions of increased mitotic activity, but these regions' mitotic figures have normal morphology and tend not to be associated with significant nuclear atypia.

Immunohistochemistry

Smooth muscle cells in the myometrium and within smooth muscle tumors retain staining with antibodies to muscle-specific actin, alpha-smooth muscle actin, desmin, and caldesmon (Eyden et al. 1992), and to a lesser degree with vimentin. ER are frequently expressed, as well as WT1 to a lesser degree; ER staining is used to determine whether extrauterine smooth muscle tumors are of gynecologic type (Lee et al. 2009). Leiomyomas frequently stain positive for cytokeratin, similar to the surrounding myometrium, the extent and intensity of reactivity depending on the antibodies used and the fixation of the specimen (Brown et al. 1987; Eyden et al. 1992; Gown et al. 1988). Epithelial membrane antigen (EMA) is usually negative in smooth muscle tumors.

Molecular Pathology

Leiomyomas are a proliferation of a single clone of smooth muscle cells, as evidenced by nonrandom inactivation of the X chromosome observable through glucose-6-phosphate dehydrogenase isoform expression and other techniques. Cytogenetic studies provide further evidence of these tumors' clonal nature (Quade 1995).

Leiomyomas' cytogenetic abnormalities have recently become the focus of much research. While early cytogenetic alterations are considered by some investigators to be insufficient for tumor development, dysregulation of multiple signaling pathways may be transformative. Pathways that may contribute to the development of leiomyomas include steroids, growth factors, transforming growth factor-beta (TGF-β)/Smad, wingless-type (Wnt)/β-catenin, retinoic acid, and vitamin D, which converge in synergistic ways (Borahay et al. 2015).

Approximately 40% of uterine leiomyomas have chromosomal abnormalities detectable by conventional cytogenetic analysis, including t(12;14)(q15;q23-24), rearrangements involving the short arm of chromosome 6, and interstitial deletions of the long arm of chromosome 7 (Lobel et al. 2006; Quade 1995; Sornberger et al. 1999). More recent work has established that, from a genomic standpoint, there are at least four mostly nonoverlapping categories of uterine leiomyomas, some of which have interesting clinicopathological correlates (Markowski et al. 2015; Mehine et al. 2013, 2014). Listed in roughly decreasing order of prevalence are mediator subcomplex 12 (*MED12)* point mutation or deletion with consequent upregulation of *RAD51B* (60–70% of cases) (Mehine et al. 2013; Quade et al. 2003; Schoenmakers et al. 1999); *high mobility group protein AT-hook 2* gene (*HMGA2*) overexpression with *RAD51B* as an enhancer (10–20% of cases); *fumarate hydratase* (*FH*) inactivation; and *COL4A6-COL4A5* deletion. *HMGA2* overexpression is due to the t(12;14)(q15;q23-24) translocation or complex rearrangements involving the *HMGA2* gene that occur in the setting of multiple interconnected rearrangements (also referred to as chromothripsis) (Markowski et al. 2015; Mehine et al. 2013). These complex chromosomal rearrangements tend to be found most often in leiomyomas lacking *MED12* mutations (Mehine et al. 2014). Rare leiomyomas with both *MED12*

and *HMGA2* abnormalities have been reported (Holzmann et al. 2015), while chromosome 7q deletions may occur with or without either *MED12* and *HMGA2* mutations (Markowski et al. 2012; Mehine et al. 2013). Chromosome 7 deletions may target yet another gene, *CUX1* (Schoenmakers et al. 2013).

Leiomyomas with *HMGA2* rearrangements usually occur as single nodules, while leiomyomas with *MED12* mutations present as multiple tumors; this has led to the hypothesis that *MED12* mutations might be present in stem-like mesenchymal cells, which can proliferate in myometrium, leading to a "leiomyoma field effect." *MED12*-mutated leiomyomas tend to be smaller than those with *HMGA2* rearrangements (Markowski et al. 2015).

Certain abnormalities cluster with specific leiomyoma subtypes. Namely, recurrent loss of 22q12.3-q13.1 is linked to IVL (Buza et al. 2014). Loss of 1p, often in combination with other aberrations, particularly loss of chromosomes 19 and/or 22, is associated with cellular leiomyoma (Christacos et al. 2006); 19q and 22q terminal deletions are often seen in benign metastasizing leiomyoma (Mehine et al. 2013); FH deficiency is linked to leiomyomas (Gross et al. 2004; Lehtonen et al. 2004; Mehine et al. 2014); and certain types of leiomyomas with bizarre nuclei, some with somatic abnormalities in the *FH* gene and rarely germline mutations as discussed subsequently (Bennett et al. 2017b; Gunnala et al. 2017).

Clinical Behavior and Treatment

Most leiomyomas are asymptomatic, and only a minority requires treatment. Therapy is indicated only if leiomyomas are symptomatic, interfere with fertility, enlarge rapidly, or pose diagnostic problems (Bukulmez and Doody 2006; Ouyang et al. 2006; Wallach and Vlahos 2004). Sometimes they can be excised (myomectomy), but if they are large or multiple, a hysterectomy may be required. Treatment with leuprolide acetate or another gonadotropin-releasing hormone agonist (GnRHa), which drastically lowers estrogen levels by causing pituitary desensitization, results in shrinkage of leiomyomas, a decrease in uterine volume, and alleviation of the patient's symptoms (Marsh and Bulun 2006; Rackow and Arici 2006; Shaw 1998). The maximum effect is noted after 8–12 weeks, but the leiomyomas increase in size again with cessation of GnRH agonist therapy. Such therapy can be used before surgery to decrease uterine size (facilitating myomectomy or permitting vaginal rather than abdominal hysterectomy) and to reduce the risk of hemorrhage during surgery. Because GnRH agonists have unpleasant side effects such as hot flashes and have the potential to reduce bone mass loss and cause cardiovascular changes, alternatives have been sought. A more direct means of reducing estrogen is by GnRH antagonists; evidence suggests that they are effective and act rapidly without causing an initial flare in steroid levels, as is caused by GnRHa (Flierman et al. 2005).

Finally, leiomyomas can be treated by uterine artery embolization, which leads to ischemia and tumor involution (Marshburn et al. 2006; Siskin et al. 2006; Spies et al. 2001). This method of treatment is of potential interest to pathologists, because (1) if a hysterectomy is subsequently necessary, there may be areas of ischemic necrosis in a leiomyoma that must be differentiated from the type of tumor cell necrosis seen in leiomyosarcoma, and (2) the embolic particles may cause confusion unless the pathologist can recognize them (Dundr et al. 2006; McCluggage et al. 2000; Weichert et al. 2005).

Morcellation (a minimally invasive/laparoscopic technique that fragments myomas within the peritoneal cavity) of leiomyosarcomas is well known to lead to aggressive recurrence within the peritoneal cavity (discussed in detail later in this chapter), but it is perhaps less well publicized that morcellated leiomyomas may also recur intraperitoneally (Tulandi et al. 2016), though the clinical course in that case is usually not aggressive. Uncontained morcellation has also been suggested to lead to iatrogenic endometriosis and adenomyomatosis (Tulandi et al. 2016).

These findings prompted a number of gynecologic societies to issue recommendations regarding the appropriate use of morcellation for leiomyomas. The consensus is that the procedure can continue to be performed, particularly in women younger than 50 years and those who desire fertility. Current recommendations advise containing the morcellation within a bag that prevents peritoneal spillage and preoperative assessment for malignancy, the presence of which would discourage morcellation (Halaska et al. 2017; Hall et al. 2015). The problem, of course, is that a diagnosis of leiomyosarcoma is rarely evident preoperatively, even with the use of endometrial biopsy and imaging. However, qualitative magnetic resonance imaging has recently been reported to have significant discriminative power in distinguishing atypical leiomyomas and leiomyosarcomas (Lakhman et al. 2017).

These recommendations then prompted a number of clinical studies that emphasized the rarity of morcellating a "fibroid" that turns out to be a leiomyosarcoma. Two studies, one of which included 10,119 patients, reported this to occur in 0.09% of such procedures (Seidman et al. 2012) (Cui and Wright 2016; Kho et al. 2016). Some practitioners still advocate for morcellation (Parker et al. 2016), especially since the procedure, when performed for leiomyomas in young women, is cost-effective and results in low rates of intra- and perioperative complications (Cui and Wright 2016).

Specific Subtypes of Leiomyoma

Most subtypes of leiomyoma are chiefly of interest in that they mimic malignancy in one or more respects. These subtypes are mitotically active leiomyoma, cellular leiomyoma, apoplectic leiomyoma (hemorrhagic cellular leiomyoma), fumarate hydratase-deficient leiomyoma, leiomyoma with bizarre nuclei, epithelioid leiomyoma, and myxoid leiomyoma. Other leiomyoma variants, vascular leiomyoma, leiomyoma with other elements, and leiomyomas with hematopoietic elements, are more curiosities than diagnostic problems.

Mitotically Active Leiomyoma

Occasionally, a typical-appearing leiomyoma in a premenopausal woman will have $\geq$5 MF/10 HPF (Figs. 9a, b); these are designated mitotically active leiomyomas (Bell et al. 1994; Dgani et al. 1998; O'Connor and Norris 1990; Perrone and Dehner 1988; Prayson and Hart 1992). The number of mitotic figures is usually 5–9 MF/10 HPF, but occasional mitotically active leiomyomas with 10–20 MF/10 HPF have been reported. Some pathologists use 15 MF/10 HPF as the upper limit for a diagnosis of mitotically active leiomyoma and use the designation "smooth muscle tumor of uncertain malignant potential" (STUMP) when proliferative rates exceed that, whereas other pathologists use 20 MF/10 HPF as the upper limit (Bell et al. 1994).

These tumors' clinical evolution is benign, even if the neoplasm is treated by myomectomy. Their increased mitotic index may result from increased progesterone levels during the secretory phase of the menstrual cycle (Kawaguchi et al. 1989) or from progestin-only birth control (Tiltman 1985). The patient's hormonal status may also contribute to the increased number of mitotic figures seen in mitotically active leiomyomas (Prayson and Hart 1992). This diagnosis must not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures, or demonstrate zones of tumor cell necrosis, as these may be signs of malignancy.

Cellular Leiomyoma

A cellular leiomyoma is one in which the cellularity is "significantly" greater than the surrounding myometrium. Less than 5% of leiomyomas fall within this category. These tumors are described macroscopically as "fish flesh," "rubbery," and "soft," whereas typical leiomyomas are firm (Oliva et al. 1995).

Hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyoma lacks tumor cell necrosis, has few mitotic figures, and lacks the moderate to severe cytologic atypia seen in leiomyosarcoma. Some cellular leiomyomas

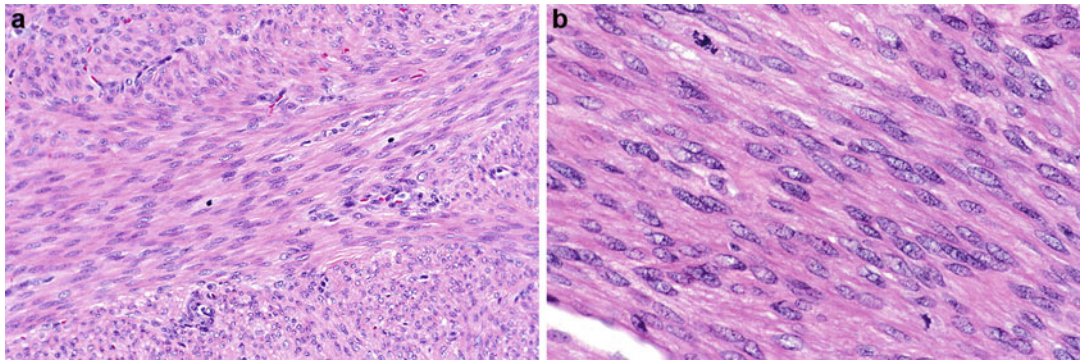

Fig. 9 Mitotically active leiomyoma. (**a**) Two mitotic figures (center) in a non-hypercellular tumor without nuclear atypia. (**b**) High magnification view of the mitotic figures in (**a**) surrounded by tumor cells of bland morphology with no necrosis

display palisading of nuclei, reminiscent of that seen in the Verocay bodies of a neurilemoma, but their ultrastructural appearance is that of an ordinary leiomyoma (Gisser and Young 1977). Prolapse of submucosal leiomyomas may result in accentuated cellularity (McCluggage et al. 1999).

Cellular leiomyomas composed of small cells with scanty cytoplasm can be difficult to distinguish from endometrial stromal tumors, especially in a "highly cellular leiomyoma" (Fig. 10) (Oliva et al. 1995). Features that help distinguish a cellular leiomyoma from a stromal tumor are the spindled shape of the cells, a fascicular growth pattern, and the absence of a plexiform vasculature. In a leiomyoma, the reticulin fibers tend to parallel the fascicles of cells, but they surround individual tumor cells in an endometrial stromal tumor. Additionally, Oliva et al. emphasized the presence of large thick-walled muscular vessels as features that serve to distinguish a highly cellular leiomyoma from a stromal proliferation (Oliva et al. 1995). Although some reports indicate that smooth muscle cells and stromal cells have immunophenotypic similarities, marked diffuse staining with muscle markers, particularly desmin (Fig. 11), is more suggestive of a smooth muscle tumor than of a stromal neoplasm (Oliva et al. 1995). Whether the lesion is invasive is best observed on a hysterectomy specimen. In the absence of myoinvasion or vascular invasion, the differential lies between two benign conditions: highly cellular leiomyoma and stromal nodule. When there is intravascular tumor,

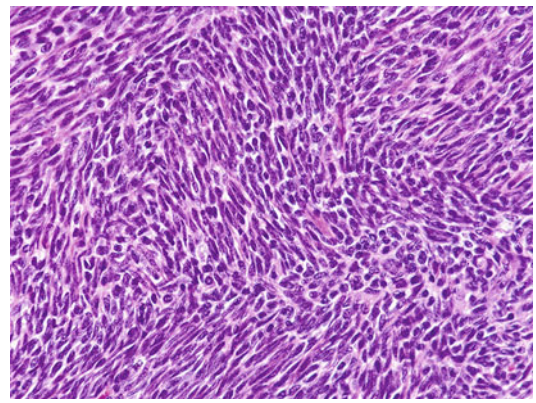

Fig. 10 Highly cellular leiomyoma. Cells are small and rounded and contain scanty cytoplasm

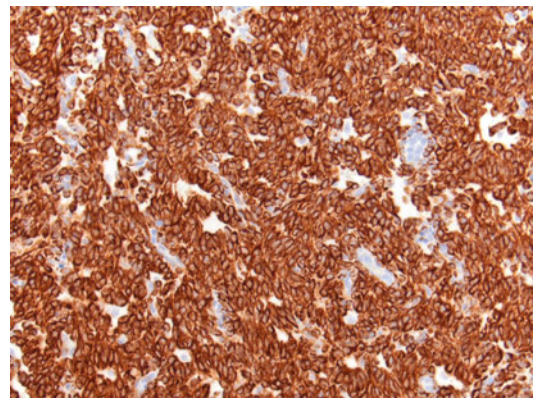

Fig. 11 Highly cellular leiomyoma. The tumor cells show strong cytoplasmic staining for desmin and immunoreactivity for smooth muscle actin and caldesmon but staining for CD10 was negative

the distinction between endometrial stromal and smooth muscle differentiation becomes clinically relevant as the differential diagnosis lies between stromal sarcoma (a clinically low-grade malignancy) and IVL (clinically benign unless there are cardiac or pulmonary complications).

When a cellular mesenchymal proliferation is recovered in an endometrial sampling, care must be taken to determine whether the growth is benign or, much more rarely, a stromal sarcoma. Three issues need to be considered: (1) what differentiation does the proliferation exhibit (smooth muscle or endometrial stromal); (2) are the criteria of malignancy evaluable; and, finally, (3) are the criteria of malignancy met? Rarely, some uterine neoplasms appear to be composed of a mixture of stromal and smooth muscle cells (Bell et al. 1994; Oliva et al. 1998, 2007); these are currently categorized as endometrial stromal neoplasms, not "mixed endometrial stromal and smooth muscle neoplasms." Regardless of the differentiation present, unequivocal diagnoses of "endometrial stromal sarcoma" on biopsy or curettage should be avoided since that would require a therapeutic hysterectomy. For older patients or young patients with no interest in having children, the issue is usually resolved by what amounts to a diagnostic hysterectomy. For premenopausal women wishing to retain fertility and older patients who are poor surgical candidates, diagnostic modalities such as hysteroscopy, imaging studies, repeat sampling, and immunohistochemistry should be considered, although conservative clinical management does not necessarily constitute the standard of care.

Apoplectic Leiomyoma (Hemorrhagic Leiomyoma)

Hemorrhagic cellular leiomyoma, or "apoplectic" leiomyoma (Bennett et al. 2016; Oliva 2016), is a form of cellular leiomyoma that may occur in women who are taking oral contraceptives or who are either pregnant or postpartum, but many exceptions to these generalizations are on record (Myles and Hart 1985; Norris et al. 1988). Grossly, these tumors frequently exhibit hemorrhage (sometimes multifocal and stellate in shape), infarct-type necrosis, cyst formation, softening, and brown-red discoloration (Fig. 12) (Bennett et al. 2016). Microscopically, the leiomyoma is cellular and contains patchy areas of hemorrhage and edema. Hemorrhagic areas are surrounded by a narrow zone resembling granulation tissue, around which the tumor cells show slightly increased number of mitotic figures. These organizing infarcts are usually easy to distinguish from the more ominous coagulative tumor cell necrosis, though early infarcts may appear similar, with abrupt transitions between viable and nonviable tissue. Nonetheless, the presence of hemorrhage and lack of significant nuclear atypia both within ghost cells and viable tumor cells should distinguish this type of infarct. In contrast to leiomyosarcoma, neither atypical mitotic figures nor significant cytologic atypia is present, and the neoplasm has a circumscribed, compressive margin.

FH-Deficient Leiomyoma

Recognition of FH-deficient leiomyomas as a distinct class followed from the discovery that hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) is underpinned by germline mutations in *FH* (Stewart et al. 2008; Toro et al. 2003; Wei et al. 2006). Women in HLRCC-affected families often develop leiomyomas before age 40. In uterine tumors from these families, the smooth muscle cells contain viral inclusion-like eosinophilic macronucleoli with peri-nucleolar halos, similar to what is seen in syndromic renal cell carcinomas (Garg et al. 2011; Sanz-Ortega et al. 2013). Studies indicating that somatic *FH* abnormalities are more common than germline mutations also identified additional characteristic features (Miettinen et al. 2016; Reyes et al. 2014). These include round-to-oval nuclei in spindled smooth muscle cells with overtly fibrillary cytoplasm that sometimes also includes globoid eosinophilic bodies, the aforementioned

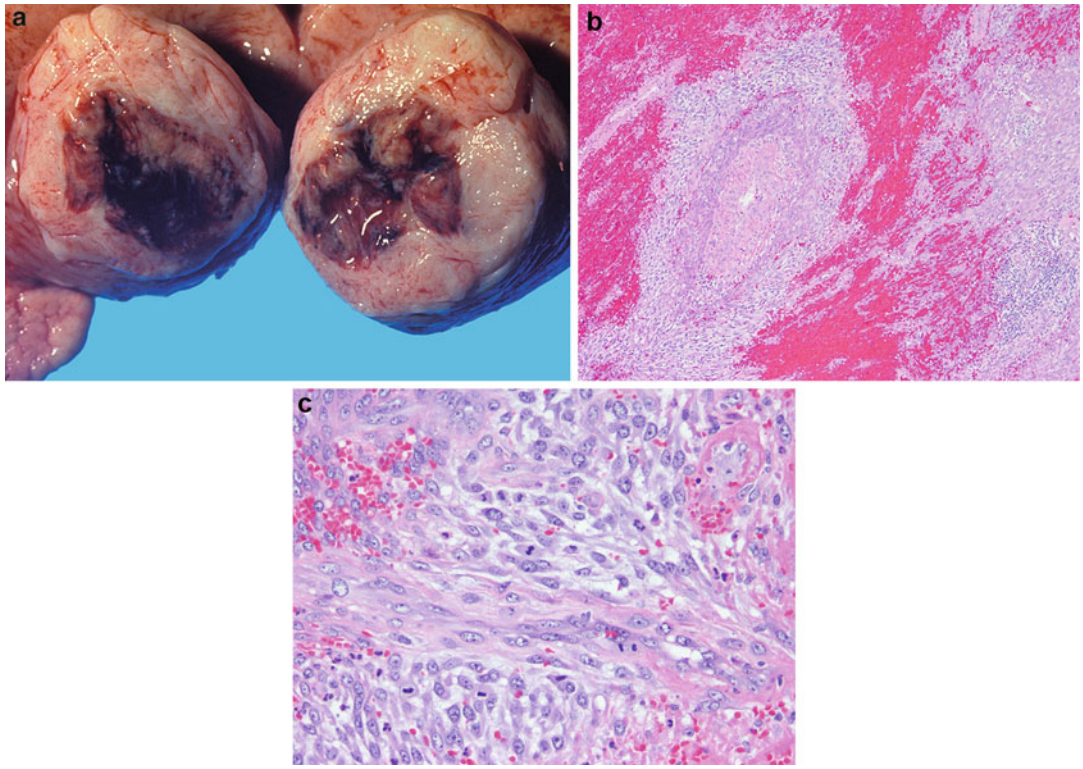

Fig. 12 **Apoplectic leiomyoma.** (**a**) Multiple foci of hemorrhage are visible on the cut surfaces of a myomectomy specimen. (**b**): "Zonation" phenomenon: Viable smooth muscle, granulation-like tissue, and hemorrhage. (**c**): Smooth muscle surrounding this hemorrhagic infarct is mitotically active. Intact leiomyoma distant from the infarct showed a low mitotic index

nuclear characteristics, and a staghorn vasculature (Fig. 13). Nuclei are sometimes arranged in more-or-less linear rows, resulting in nuclear-dense and nuclear-free zones, somewhat reminiscent of "neurilemomatous leiomyoma."

These features are characteristic of FH-deficient leiomyoma, but they may not be specific to tumors carrying *FH* mutations (Alsolami et al. 2014; Miettinen et al. 2016; Reyes et al. 2014). Immunohistochemical stains can identify loss of FH protein (commercially available anti-FH antibodies) or the downstream metabolic changes associated with FH loss (antibodies against 2-succinyl cysteine, a protein modification caused by FH deficiency) (Bardella et al. 2011; Buelow et al. 2016; Joseph et al. 2015). These cells' aberrations in the mitochondrial enzyme *FH* are thought to make them depend more heavily on glycolysis for their energy needs; this has been named the "Warburg effect" (Warburg 1956). Although the Warburg effect is now usually thought of as an epiphenomenon or a downstream effect of oncogenes or tumor suppressor genes in other tumor types, in FH-deficient tumors, it likely has direct oncologic manifestations (Yang et al. 2012), perhaps through protein succination or fumarate accumulation.

Patients with HLRCC may develop multiple cutaneous and uterine leiomyomas and an aggressive form of renal carcinoma that has been described as part of the spectrum of type II papillary renal cell carcinoma (Launonen et al. 2001; Tomlinson et al. 2002). As cutaneous and uterine leiomyomas may be sentinel disease manifestations, their recognition could enable early diagnosis of potentially lethal renal cell carcinomas. Cutaneous and uterine leiomyomas are present in 75% and 80% of HLRCC patients, respectively (Lehtonen et al. 2006; Sanz-Ortega et al. 2013; Toro et al. 2003; Wei et al. 2006), but in

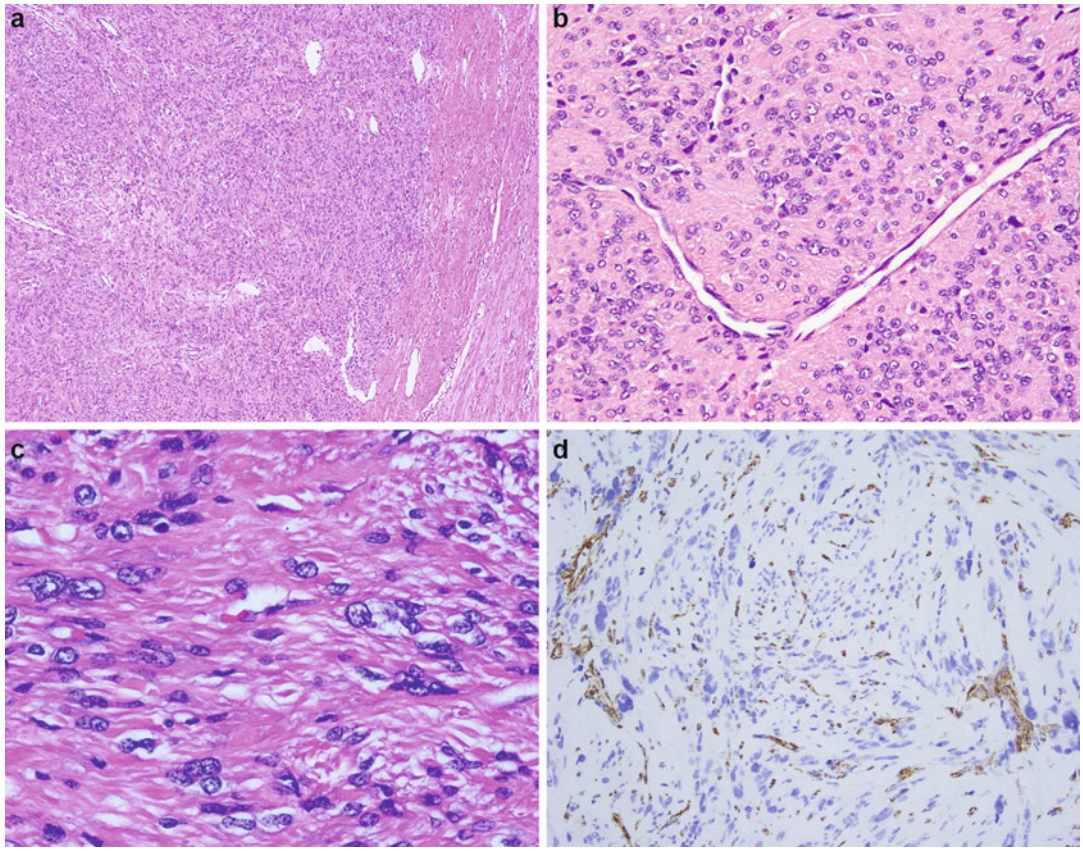

Fig. 13 FH-deficient leiomyoma. (**a**) The tumor is more cellular than surrounding myometrium and contains fusiform cells with oval nuclei and a staghorn vasculature. Nuclear-free and nuclear-dense zones can be appreciated. (**b**) Intermediate power magnification emphasizing the staghorn vasculature. (**c**) High power magnification reveals round nuclei with prominent eosinophilic nucleoli with perinuclear clearing and eosinophilic cytoplasmic globules. (**d**) Tumor cells are negative for FH, while expression is retained in normal constituents

40% of patients with cutaneous leiomyomas, the tumors' presentation is subtle (Toro et al. 2003; Wei et al. 2006). Cutaneous leiomyomas typically present around 25 years of age, whereas uterine leiomyomas are characteristically multiple and occur at a mean age of 30 years. Renal cell carcinomas are present in only 20–30% of kindreds and occur at an average age of 46 years (Gardie et al. 2011; Merino et al. 2007). HLRCC is therefore an incompletely penetrant syndrome, with a wide spectrum of disease ranging from asymptomatic to lethal.

Somatic *FH* abnormalities, which may affect as few as 2–3% of leiomyomas, are far more common than germline mutations. When deciding which patients should be considered for germline genetic testing, one must account for not only the immunohistochemical and morphological features of the uterine leiomyoma but also the patient's characteristics. Patients who have a large FH-deficient leiomyoma and present before 35–40 years of age are most likely to have a germline mutation, especially when cutaneous leiomyomas are also present.

Leiomyoma with Bizarre Nuclei

Several different terms have been used to describe leiomyomas with bizarre nuclei, including

symplastic leiomyoma and atypical leiomyoma (Bennett et al. 2017b; Croce et al. 2014; Ly et al. 2013).

Microscopically, leiomyoma with bizarre nuclei is distinguished by moderate to severe cytologic atypia, a feature shared with malignant uterine smooth muscle tumors, but in this case high mitotic activity (>10 MF/HPF) and tumor cell necrosis are absent (Bell et al. 1994; Downes and Hart 1997). The atypical cells may be distributed throughout the leiomyoma or they may be focal; they have enlarged hyperchromatic nuclei with prominent chromatin clumping and, often, smudging (Fig. 14), as well as large cytoplasmic pseudonuclear inclusions. Multinucleated tumor giant cells can be numerous and prompt the name "bizarre" or "symplastic" leiomyoma.

Mitotic counting in these tumors may be complicated by the frequent presence of bizarre-appearing karyorrhexis and pyknotic nuclei that mimic the appearance of highly atypical mitotic figures. Recognition of true mitotic figures can be facilitated with a phosphohistone-H3 immunohistochemical stain (Chow et al. 2017; Veras et al. 2009), but even when relying on this stain, only figures that resemble mitoses should be counted. When performing a traditional mitotic count using hematoxylin and eosin (H&E), it is often helpful to carefully assess areas of the tumor that are not overtly bizarre in appearance. If mitotic activity is readily apparent in these areas, the lesion in question may not be best diagnosed as leiomyoma with bizarre nuclei. Scrutiny of such areas may also reveal the presence of a population of monomorphic, enlarged and

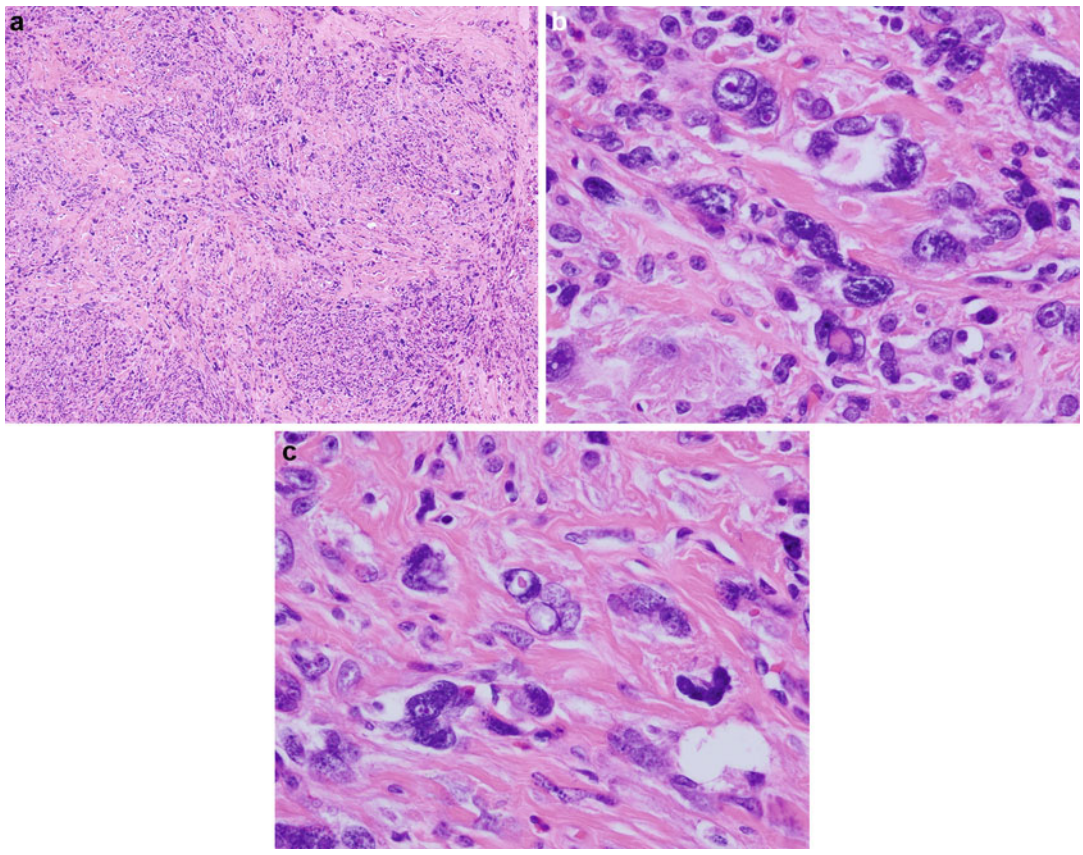

Fig. 14 Leiomyoma with bizarre nuclei. (**a**) Atypical cells are distributed throughout. (**b**) Tumor cells have single or multiple pleomorphic nuclei with coarse, smudged chromatin. (**c**) High power magnification reveals prominent eosinophilic nucleoli with perinuclear clearing, suggesting that this bizarre leiomyoma is FH deficient

hyperchromatic nuclei; a mitotic index of >10 MF/HPF in these areas would place the tumor in the leiomyosarcoma category.

Because leiomyosarcomas can vary greatly in appearance and may contain areas that lack the typical features of hypercellularity, cytologic atypia, and increased mitotic activity, extensive sampling is important to rule out that diagnosis. Leiomyoma with bizarre nuclei is less common in postmenopausal women, so a careful search for other features of leiomyosarcoma is indicated when a smooth muscle tumor containing atypical cells is detected in an older woman. This is especially important in consideration of the possibility that leiomyoma with bizarre nuclei may represent a precursor to leiomyosarcoma (Mittal and Joutovsky 2007; Mittal et al. 2009). To detect such cases, one must liberally sample and carefully examine both pleomorphic portions of the tumor for increased mitoses and spindle cell areas for nuclear enlargement and hyperchromasia, elevated mitotic index, and coagulative tumor cell necrosis.

The clinical course of smooth muscle neoplasms featuring mitotic indices of less than 10 MF/10 HPF that lack tumor cell necrosis and that exhibit diffuse moderate to severe atypia remains controversial. In one series of 24 such cases, all had a benign clinical course (Downes and Hart 1997), while another series of 43 cases, all of which had at least 2 years follow-up, included only a single malignancy (2%), though progression took place over several years, which is much slower than in leiomyosarcoma (Bell et al. 1994). The latter study included only uterine smooth muscle neoplasms with moderate to severe atypia, a mitotic index less than 10 MF/10 HPF, and without tumor cell necrosis. In a subsequent study of patients whose tumors had less than 4 MF/10 HPFs (Ly et al. 2013), recurrences were rare. Only one patient (<2% of the study group) experienced an extrauterine recurrence at 7 years, unlike most leiomyosarcomas where recurrences typically present no later than 5–6 years after initial diagnosis.

Genetic and morphological heterogeneity within bizarre leiomyoma was originally suggested by studies that divided the tumor subtype into two subsets, with one frequently displaying aberrant p53 staining (Croce et al. 2014; Zhang et al. 2014). Recent reports confirm that leiomyomas with bizarre nuclei can be divided into two genomic subtypes, each with a unique set of genetic, immunohistochemical, and morphological features; one subset is characterized by *FH* aberration, while the other carries *Tp53* and/or retinoblastoma (*RB*) abnormalities (Bennett et al. 2017b; Ubago et al. 2016; Zhang et al. 2017). Tumors harboring *FH* abnormalities display characteristic histological features seen in FH-deficient leiomyomas, along with positive 2SC staining and loss of FH staining, as described above. Massively parallel sequencing revealed that almost all tumors with an aberrant FH/2SC immunoprofile harbored somatic *FH* genetic alterations, including homozygous deletions (most commonly), missense mutations coupled with loss of heterozygosity, and a splice site mutation (Bennett et al. 2017b). Leiomyomas with bizarre nuclei with normal FH/2SC staining more frequently harbored *TP53* and/or *RB1* alterations.

Epithelioid Leiomyoma

Epithelioid leiomyomas include tumors formerly classified as leiomyoblastoma, clear cell leiomyoma, and plexiform leiomyoma (Kurman and Norris 1976). Epithelioid smooth muscle tumors have the same histologic appearance in the uterus as in other sites in the body. The mean age of incidence is in the fifth decade, with a range of 30–78 years (Kurman and Norris 1976; Prayson et al. 1997). Epithelioid leiomyomas are yellow or gray, may contain areas of hemorrhage, and tend to be softer than the usual leiomyoma. Most are solitary, and they can occur in any part of the uterus. The median diameter is 6–7 cm.

Microscopically, the cells are round or polygonal rather than spindle-shaped and are arranged in clusters or cords. The nuclei are round, relatively large, and centrally positioned. The three leiomyoma variants that now compose epithelioid leiomyoma are leiomyoblastoma, clear cell leiomyoma, and plexiform leiomyoma. Mixtures of the various patterns are common, providing the

basis for designating all of these as epithelioid leiomyomas. Leiomyoblastoma is composed of round cells with eosinophilic cytoplasm (Fig. 15) rather than spindle cells. Clear cell leiomyoma consists of polygonal cells with abundant clear cytoplasm and well-defined cell membranes (Fig. 16), which may contain glycogen, though lipid content is minimal and mucin is absent. The nucleus sometimes is displaced to the periphery of the cell, resulting in a signet-ring appearance. Plexiform leiomyoma is characterized by cords or nests of round cells with scanty to moderate amounts of cytoplasm. Transition to more typical spindled smooth muscle cells is often identified within an epithelioid leiomyoma. Immunohistochemical stains confirm the myogenous phenotype of the tumor cells (Brooks et al. 1992; Devaney and Tavassoli 1991; Hyde et al. 1989; Rizeq et al. 1994). Ultrastructural examination reveals features of smooth muscle differentiation such as parallel cytoplasmic filaments, dense bodies, and basal lamina production (Chang et al. 1977; Hyde et al. 1989; Ito et al. 1986; Mazur and Priest 1986), and in some clear cell leiomyomas, numerous mitochondria or cytoplasmic vacuoles.

Small plexiform leiomyomas that are detected only on microscopic examination are referred to as plexiform tumorlets (Fig. 17) (Kaminski and Tavassoli 1984). These lesions were formerly thought to be angiomas or endometrial stromal tumors, but ultrastructural examination revealed myofilaments and other features of smooth muscle cells (Kaminski and Tavassoli 1984; Nunez-Alonso and Battifora 1979), and the cells have a myogenous immunophenotype (Devaney and Tavassoli 1991). Plexiform tumorlets are usually submucosal, but they can occur anywhere in the myometrium and even in the endometrium. Most are solitary but sometimes they may be multiple (Seidman and Thomas 1993).

While many epithelioid smooth muscle neoplasms of the uterus are generally regarded as benign, the rarity of these tumors limits the predictability of their clinical course (Clement 2000; Kurman and Norris 1976; Prayson et al. 1997). Benign epithelioid tumors include plexiform tumorlets as well as small lesions that lack

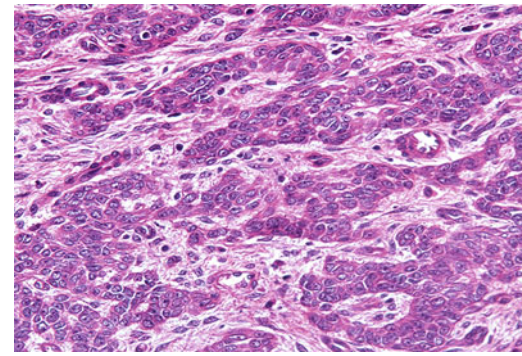

Fig. 15 Epithelioid smooth muscle tumor. Cellular tumor composed of poorly cohesive polygonal cells with eosinophilic cytoplasm

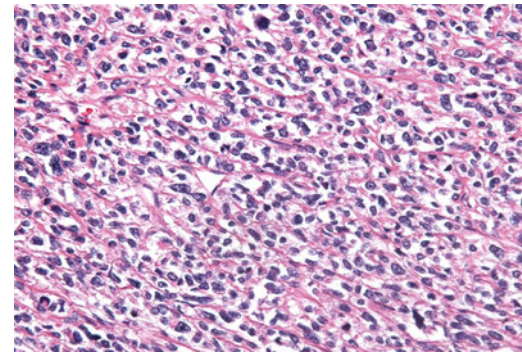

Fig. 16 Clear cell variant of epithelioid leiomyoma. Nests of cells with abundant clear cytoplasm

cytologic atypia, tumor cell necrosis, and an elevated mitotic index or that display circumscribed margins, extensive hyalinization, and predominance of clear cells. The behavior of epithelioid leiomyomas with two or more of the following features is not well established: large size (greater than 6 cm), moderate mitotic activity (2–4 MF/10 HPF), moderate to severe cytologic atypia, and necrosis. Epithelioid leiomyomas with moderate to severe atypia, without necrosis, and fewer than 5 MF/10 HPF are classified as "STUMP" and warrant careful follow-up.

While experience with these tumors is limited, some potential indicators of malignancy have been identified. Neoplasms with 5 or more MF/10 HPF metastasize frequently enough that all should be regarded as epithelioid

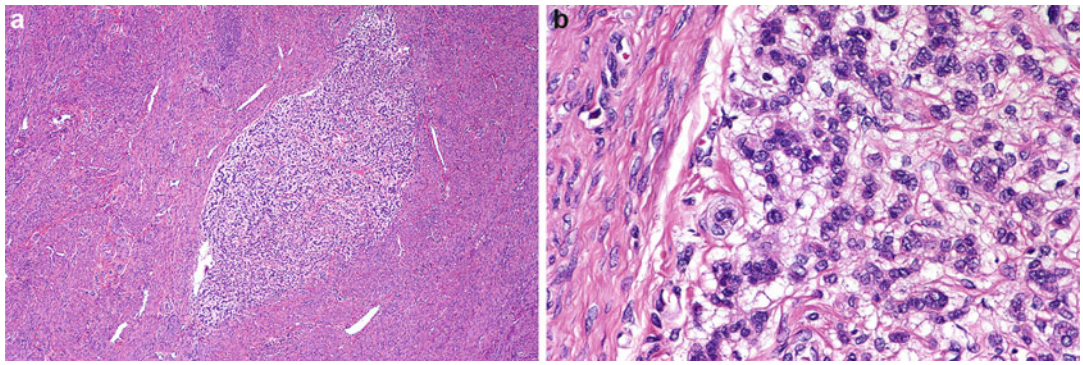

Fig. 17 Plexiform tumorlet. This microscopic tumor is completely surrounded by normal myometrium (**a**) and consists of serpiginous cords of epithelioid smooth muscle cells (**b**)

leiomyosarcomas, even in the absence of cytologic atypia and tumor cell necrosis (Jones and Norris 1995; Kurman and Norris 1976). All epithelioid tumors with tumor cell necrosis reviewed at Stanford have been clinically malignant (Atkins et al. 2001).

Most malignant epithelioid smooth muscle tumors are of the leiomyoblastoma type, although clear cell leiomyosarcoma has been reported (Silva et al. 1995). The epithelioid appearance of these neoplasms raises a broad differential including PEComa (muted desmin expression with melanoma-associated marker positivity and, sometimes, *TFE3* overexpression), metastatic (or locally invasive) carcinoma (cytokeratin positivity), metastatic melanoma (S-100 positive), placental site and epithelioid trophoblastic tumors (GATA-3 positive), and ASPS (HMB-45 negative with *Xp11* translocation). Some endometrial stromal neoplasms may have an epithelioid appearance (Lee et al. 2012b).

Myxoid Leiomyoma

Myxoid leiomyomas are extremely rare and should be considered a diagnosis of exclusion. The differential diagnosis includes hydropic leiomyoma (edema fluid, not stromal mucin) (Clement et al. 1992), myxoid leiomyosarcoma, myxoid change (Pugh et al. 2012), inflammatory fibromyxoid tumor (*ALK*-rearranged) (Bennett et al. 2017a; Parra-Herran et al. 2015; Rabban et al. 2005), and myxoid/fibromyxoid variants of endometrial stromal sarcoma (Lewis et al. 2017; Oliva et al. 1999; Yilmaz et al. 2002).

Macroscopically, myxoid leiomyomas are soft and translucent. Microscopically, they contain abundant amorphous myxoid material between the smooth muscle cells (Mazur and Kraus 1980). The margins of a myxoid leiomyoma are circumscribed, and neither cytologic atypia nor mitotic figures are present. Further criteria for this diagnosis are small, uniform cells, absent or mild atypia, no more than 2 MF/10 HPF, and foci of ordinary leiomyoma. Large myxoid smooth muscle tumors and those in which an infiltrating margin, cytologic atypia, or mitotic activity are observed microscopically should be regarded with suspicion. Some myxoid smooth muscle tumors exhibiting these features are clinically malignant even though they do not meet standard criteria for a diagnosis of leiomyosarcoma. Enlarged, atypical cells are an ominous finding. Focal mild atypia, in combination with infiltrative growth, even in the absence of tumor cell necrosis and high mitotic activity, may be sufficient to diagnose myxoid leiomyosarcoma; in a small series of nine such tumors, five recurred (Burch and Tavassoli 2011).

Vascular Leiomyoma

Vascular leiomyomas contain numerous large-caliber vessels with muscular walls and can be difficult to distinguish from a hemangioma or an arteriovenous malformation if the vascular

component predominates. However, unlike these growths, which are poorly defined, vascular leiomyomas are clearly circumscribed neoplasms that contain at least foci of typical spindled smooth muscle cells. Another helpful distinction is that hemangiomas, which are very rare in the uterus, are usually of the cavernous type.

Leiomyoma with Other Elements

Several types of differentiation have been identified in leiomyomas, but the most common is fatty differentiation, with fairly regularly encountered adipocytes scattered within an otherwise typical leiomyoma. A leiomyoma that contains a striking amount of fat is called a lipoleiomyoma (Fig. 18); if a vascular component is also present, it is designated as an angiolipoleiomyoma. Most such tumors occur in middle-aged or elderly women and may arise in any part of the uterus, including the cervix, and broad ligament (Wang et al. 2006). They average 6 cm in diameter and have soft yellow areas on the cut surface. Fat cells are generally found in circumscribed areas within the leiomyoma but may be present diffusely. In most instances, the smooth muscle component is composed of spindled cells, though lipomatous components may also arise within other tumor subtypes such as epithelioid leiomyoma; fatty change is common in IVL (Brooks et al. 1992). In at least one case, lipoleiomyoma has involved complex cytogenetic abnormalities (Pedeutour et al. 2000). Only a few pure lipomas have been described in the uterus (Dharkar et al. 1981; Pounder 1982), and similarly liposarcoma like lipoleiomyoma is rare (McDonald et al. 2011; Schoolmeester et al. 2016). Other tissue types that have been reported within leiomyomas include brown fat, skeletal muscle, and cartilage (Chen 1999; Fornelli et al. 1999; Martin-Reay et al. 1991; Yamadori et al. 1993).

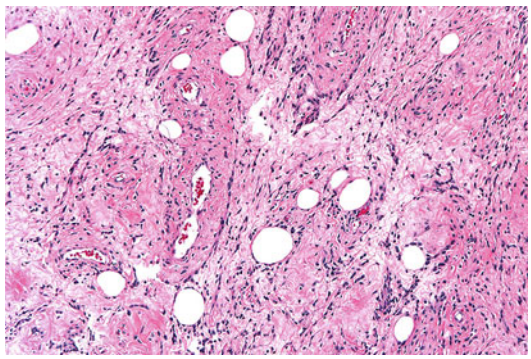

Fig. 18 Lipoleiomyoma. The tumor is composed of an intermixture of fat cells, smooth muscle, and collagen

Leiomyoma with Hematopoietic Cells

Large numbers of hematopoietic cells, which sometimes have no obvious etiology, may infiltrate leiomyomas. These infiltrations are distinct from abscesses, which can arise in bacterially infected leiomyomas. Peculiar infiltrates include extramedullary hematopoiesis in the absence of systemic disease (Schmid et al. 1990), a prominent histiocytic infiltrate (Adany et al. 1990), a prominence of mast cells or eosinophils (Crow et al. 1991; Maluf and Gersell 1994; Orii et al. 1998; Vang et al. 2000), and, most importantly, a dense lymphoid infiltrate that can mimic lymphoma (Ferry et al. 1989).

Smooth Muscle Proliferations with Unusual Growth Patterns

Diffuse Leiomyomatosis and Myometrial Hypertrophy

Diffuse leiomyomatosis is an unusual condition in which innumerable small smooth muscle nodules produce symmetric enlargement of the uterus. The uterus may be greatly enlarged, weighing up to 1000 g. The smooth muscle nodules range from microscopic to 3 cm in size, but most are less than 1 cm in diameter. They are composed of uniform, bland, spindled smooth muscle cells and are less circumscribed than typical leiomyomas. The clinical course may be complicated by hemorrhage, but the condition is benign (Clement 2000; Grignon et al. 1987; Lai et al. 1991; Mulvany et al. 1995).

Myometrial hypertrophy is a condition in which the myometrium is thickened and the uterus is symmetrically enlarged. No specific gross or microscopic abnormality is noted; the uterus is

abnormal in size (>130 g for nulliparous, >210 g for parity 1–3, and > 250 g for parity of 4 and above) only (Langlois 1970). Uterine weight increases with age and with increasing parity until menopause and decreases after.

Dissecting Leiomyoma

Dissecting leiomyoma refers to a benign smooth muscle proliferation where the border consists of compressive tongues of smooth muscle that penetrate into the surrounding myometrium and, occasionally, into the broad ligament and pelvis (Roth and Reed 1999). This pattern of infiltration may also be seen in IVL (see following). When edema and congestion are prominent, a uterine dissecting leiomyoma with extrauterine extension may resemble placental tissue, hence the name cotyledonoid dissecting leiomyoma (Fukunaga and Ushigome 1998; Roth and Reed 2000; Roth et al. 1996) (Fig. 19).

IVL and Leiomyoma with Vascular Invasion

IVL is a very rare smooth muscle tumor characterized by nodular masses of histologically benign smooth muscle cells growing within venous channels (Clement 1988; Cohen et al. 2007; Mulvany et al. 1994; Nogales et al. 1987; Norris and Parmley 1975). These tumors affect women at a median age of 45 years; few patients with IVL are younger than 40 years. The condition is not associated with a history of infertility or decreased parity and affects all ethnicities equally. The main symptoms are abnormal bleeding and pelvic discomfort, and most patients present with a pelvic mass.

Grossly, IVL is a complex coiled or nodular growth within the myometrium with convoluted, wormlike extensions into the uterine veins in the broad ligament or into other pelvic veins (Fig. 20). The growth extends into the vena cava in more than 10% of patients, and in some it reaches as far as the heart (Clement 1988; Cohen et al. 2007; Kokawa et al. 2002; Suginami et al. 1990). The wormlike masses vary from soft and spongy to rubbery and firm, and their color is pink-white or gray. Intravenous growth with an IVL-like pattern has been described in leiomyosarcoma (Coard and Fletcher 2002), so it is important to carefully assess any such growth for features that might signify malignancy (high mitotic rate, significant nuclear atypia, tumor cell necrosis). As mentioned previously, IVL may have a peculiar karyotype, showing recurrent loss of 22q12.3-q13.1 (Buza et al. 2014).

Microscopically, IVL is found within venous channels lined by endothelium (Fig. 21). They have a highly variable histologic appearance, even within the same tumor. Some have a similar cellular composition to that of a

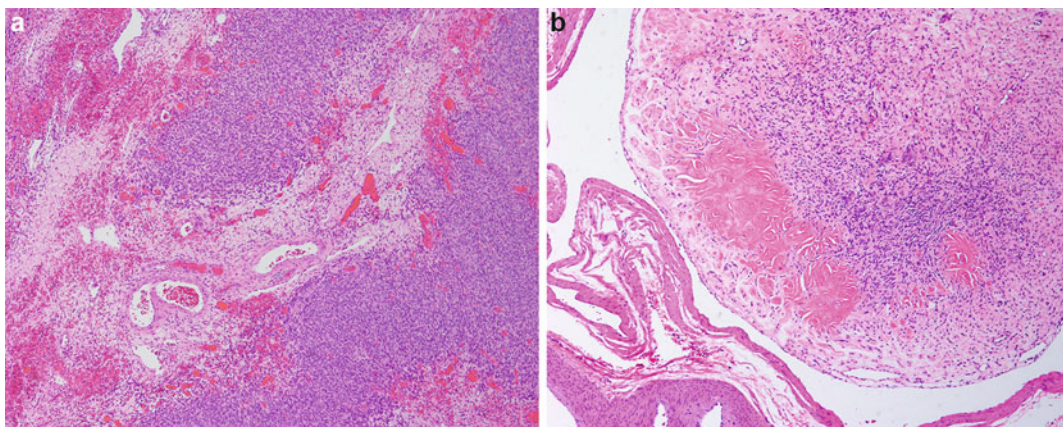

Fig. 19 Dissecting leiomyoma. (**a**) In broad ligament, (**b**) associated with IVL (Fig. 21)

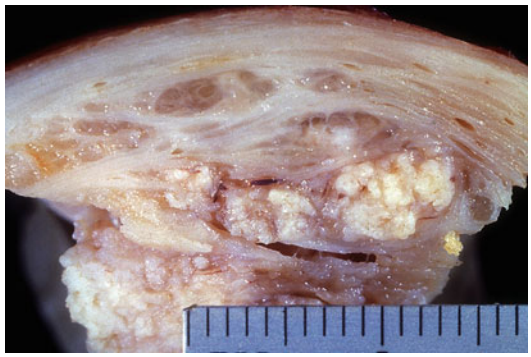

Fig. 20 IVL. Brown and white plugs of intravascular tumor grow extensively in the myometrium

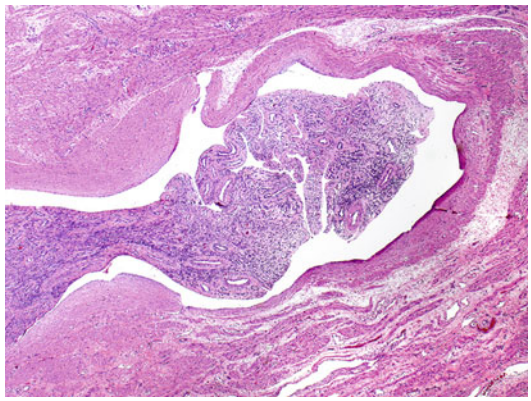

Fig. 21 IVL. A plug of smooth muscle tumor grows within a large vein in the myometrium

leiomyoma, but most contain prominent zones of fibrosis or hyalinization, sometimes making smooth muscle cells inconspicuous and difficult to identify. Cells within IVLs display the same range of smooth muscle differentiation as in a leiomyoma (Clement 1988). The intravenous growth is itself highly vascular (Fig. 22), and in some cases contains so many small and large blood vessels that it may resemble a vascular tumor. Cellular, atypical, epithelioid, and lipoleiomyomatous growth patterns have all been described; these have the same behavior and prognosis as ordinary IVL (Brescia et al. 1989; Clement 1988; Han et al. 1998).

IVL can originate in vascular smooth muscle (Norris and Parmley 1975); in these cases, the tumor is predominantly or entirely intravascular, with many sites of attachment to the vein walls.

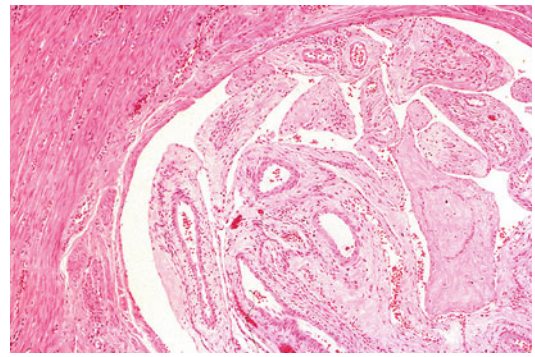

Fig. 22 IVL. Nearly the entire tumor lies within vascular spaces. The tumor is itself highly vascular and extensively hyalinized

Others develop by intravascular extension from a leiomyoma (Nogales et al. 1987; Norris and Parmley 1975), in which cases the bulk of the tumor is extravascular and sites of origin from a vein wall are not found.

IVL is treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy together with excision of any extrauterine extensions. The condition has a favorable prognosis even when tumors are incompletely excised (Mulvany et al. 1994), as pelvic recurrence is infrequent and usually amenable to surgical excision (Evans et al. 1981; Norris and Parmley 1975). Residual pelvic tumor may remain stable, but progressive growth is possible, especially in women whose treatment does not include bilateral salpingo-oophorectomy because IVL is hormonally dependent. Long-term survival is possible even after removal of plugs of tumor from the vena cava or right atrium or excision of nodules from the lung. In one case, leuprolide acetate induced tumor regression and rendered debulking surgery feasible in a patient with previously unresectable, widespread, retroperitoneal IVL (Tresukosol et al. 1995).

Benign Metastasizing Leiomyoma

Benign metastasizing leiomyoma is a nebulous condition in which "metastatic" smooth muscle tumor deposits in extrauterine locations appear to be derived from a benign leiomyoma of the

uterus. These tumors most commonly affect the lung, followed by the lymph nodes and abdomen. One or multiple nodules of a low-grade smooth muscle tumor grow in an expansile pattern within the pulmonary parenchyma, often incorporating bronchioles (Fig. 23a, b).

Almost all cases of benign metastasizing leiomyoma occur in women, most with a history of pelvic surgery. Because the primary neoplasm, typically removed years before the metastatic deposits are detected, often has been inadequately studied, reports of this condition are often difficult to assess. In some cases, the cytologic appearance, including mitotic counts, is not recorded for either the primary tumor or the alleged metastasis. A few examples may represent deportation metastases from IVL that reach the lungs, where they become implanted and grow as multiple intrapulmonary nodules of smooth muscle (Lee et al. 2008). Others may represent a multifocal smooth muscle proliferation involving the uterus and extrauterine sites (Cho et al. 1989). In the past, most examples of "benign metastasizing leiomyoma" have been interpreted as either a primary benign smooth muscle lesion of the lung in a woman with a history of uterine leiomyoma or pulmonary metastases from a morphologically non-informative smooth muscle neoplasm of the uterus (Bell et al. 1994; Cohen et al. 2007; Gal et al. 1989; Wolff et al. 1979). However, the findings of a cytogenetic study were consistent with a monoclonal origin of both uterine and pulmonary tumors with the interpretation that the pulmonary tumors were metastatic (Tietze et al. 2000). Similarly, benign metastasizing leiomyoma has been reported to have a karyotype that partly overlaps with cellular leiomyoma (19q and 22q terminal deletion) (Mehine et al. 2013).

Benign metastasizing leiomyoma may be hormonally dependent, as suggested by the expression of ER and PR in metastatic deposits (Jautzke et al. 1996) and the regression of tumors during pregnancy (Horstmann et al. 1977), after menopause, and after oophorectomy (Abu-Rustum et al. 1997). On radiography, these tumors usually appear as solitary or multiple pulmonary nodules, and on CT these nodules (or those in other organs) enhance homogeneously (Cohen et al. 2007).

Peritoneal Leiomyomas ("Parasitic" Leiomyomas)

On rare occasions, leiomyomas have been reported to "detach" from their initial subserosal location and "attach" to some other pelvic site. This improbable event presumably occurs through a combination of infarction and inflammatory adhesions. A diagnosis of parasitic leiomyoma should be made with great caution because clinically malignant smooth muscle neoplasms arising in the retroperitoneum or gastrointestinal tract are notorious for being bland and having a low mitotic index. As mentioned

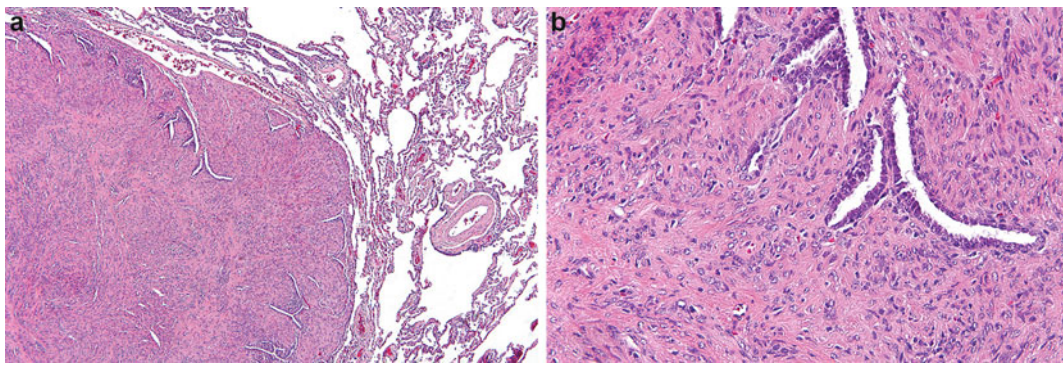

Fig. 23 Benign metastasizing leiomyoma. (**a**) A circumscribed smooth muscle tumor is present in the lung. (**b**) At high magnification, incorporated bronchioles are surrounded by cytologically bland smooth muscle cells

previously, ascertaining ER expression helps determine whether an extrauterine tumor is of gynecologic origin.

Disseminated Peritoneal Leiomyomatosis

Disseminated peritoneal leiomyomatosis (DPL) is a rare condition characterized by the presence of multiple smooth muscle, myofibroblastic, and fibroblastic nodules on the peritoneal surfaces of the pelvic and abdominal cavities in women of reproductive age (Minassian et al. 1986; Tavassoli and Norris 1981). Most cases are associated with pregnancy, an estrinizing granulosa tumor, oral contraceptive use (Tavassoli and Norris 1981), or endometriosis (Clement 2007). The most common presentation is as an unexpected finding at the time of cesarean section. DPL appears as multiple, small, granular white or tan nodules on the pelvic and abdominal peritoneum, on the surfaces of the uterus, adnexa, intestines, and in the omentum (Fig. 24a, b). The nodules are distributed randomly, and most are less than 1 cm in diameter; this contrasts with metastatic leiomyosarcoma, in which the nodules tend to be fewer, larger, and invasive into adjacent tissues.

Microscopically, DPL nodules consist of collagen, fibroblasts, myofibroblasts, smooth muscle cells, and, in pregnancy or the postpartum period, decidual cells (Fig. 25). Spindle cells usually dominate, leading to potential confusion with metastatic sarcoma, but their different clinical presentations and cellular morphologies should clearly distinguish the two. Another key distinction is that mitotic figures are infrequent in DPL, and nuclear atypia and pleomorphism are minimal or absent. Most nodules are composed of smooth muscle and decidual cells, although some are mixtures of decidua and fibroblasts or myofibroblasts, as shown by electron microscopic studies (Goldberg et al. 1977; Nogales et al. 1978; Pieslor et al. 1979; Tavassoli and Norris 1981).

DPL likely arises from a single transformation event, as indicated by a cytogenetic study. In each of the four patients, the same parental X chromosome was nonrandomly inactivated in all tumorlets (7–14 per patient), consistent with a metastatic unicentric neoplasm or, alternatively, selection for an X-linked allele in clonal multicentric lesions (Quade et al. 1997). In this regard, DPL more closely resembles IVL than typical uterine leiomyomas (Quade et al. 2002).

Consistent with its association with hormonal stimuli, biochemical or immunohistochemical methods reveal ER and PR expression within the tumorlets (Due and Pickartz 1989). DPL generally regresses or remains static after removal of the hormonal stimulus (i.e., after delivery), so radical attempts at excision are unnecessary (Tavassoli and Norris 1981). In keeping with a hormonally dependent process, DPL may regress during therapy with a

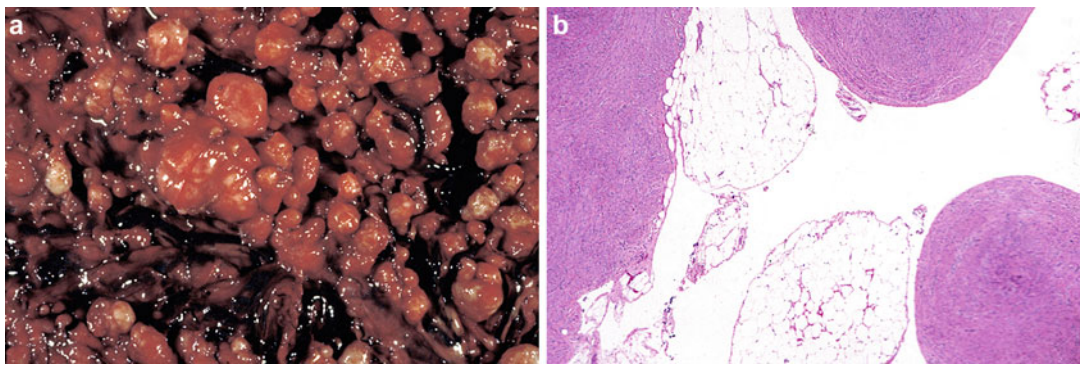

Fig. 24 DPL. Presents grossly as multiple or numerous small nodules of smooth muscle in the omentum (**a**) or on the peritoneum. A low-power photomicrograph illustrates multiple nodules of smooth muscle cells surrounded by omental fat (**b**)

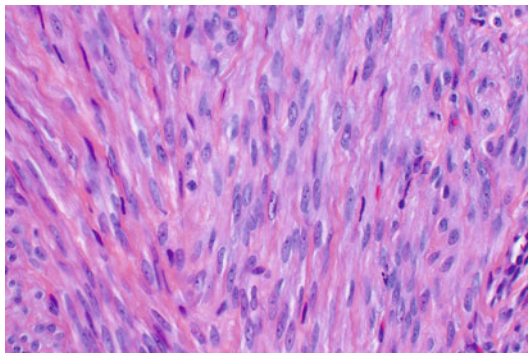

Fig. 25 DPL. The peritoneal nodules consist of histologically bland spindle-shaped smooth muscle cells; mitotic figures are absent

GnRH agonist (Hales et al. 1992) and may enlarge again when the GnRH agonist is discontinued or if the patient becomes pregnant.

In a few cases of DPL, leiomyosarcoma was diagnosed shortly after (Bekkers et al. 1999). These may represent a distinct entity, as several were distinguished from typical cases of DPL by lack of exposure to estrogen or associated uterine leiomyomas and by absence of ER and PR.

Abdominopelvic Implantation of Leiomyoma Following Morcellation

Implantation of leiomyomas following morcellation, a rare event, has been described in the literature (Seidman et al. 2012; Tulandi et al. 2016). This condition is distinct from DPL because in this setting, implantation is iatrogenic, whereas tumor spread in DPL is likely to be hormonally driven (Hales et al. 1992; Tavassoli and Norris 1982). Another difference from DPL is that no long-term studies of abdominopelvic implantation of leiomyoma following morcellation have yet been performed, whereas the clinical presentation and course of DPL is well understood. Unfortunately, several cases of abdominopelvic implantation have been described in the literature under the term "DPL." The clinical biology is currently thought to be benign provided that the histological features of the abdominopelvic tumors are those of leiomyoma. Patients can be managed with surgical resection with or without hormonal agents.

Leiomyosarcoma

Leiomyosarcoma represents about 1.3% of uterine malignancies and more than 50% of uterine sarcomas, excluding carcinosarcoma (Abeler et al. 2009). Approximately 1 of every 800 smooth muscle tumors of the uterus is a leiomyosarcoma, but fewer than 1% of women with clinically suspected leiomyoma prove to have leiomyosarcoma (Leibsohn et al. 1990).

Clinical Features

The median age of women with leiomyosarcoma is 50–55 years (Abeler et al. 2009; Giuntoli et al. 2003), nearly a decade older than women with leiomyomas, although the disease also affects women in the third decade of life. Leiomyosarcoma is more prevalent in African American women than in white women (Brooks et al. 2004) and has no relationship with gravidity or parity. The clinical presentation is nonspecific; patients present with abnormal vaginal bleeding, lower abdominal pain, or a pelvic or abdominal mass (Giuntoli et al. 2003). The average duration of symptoms before diagnosis is 5 months (Larson et al. 1990). Though a rapidly enlarging uterine smooth muscle neoplasm was previously thought to be indicative of leiomyosarcoma, the evidence does not bear out this dogma. In one study, only 1 of 371 women with a rapidly growing tumor proved to have a leiomyosarcoma (Parker et al. 1994). Unlike carcinosarcoma (malignant mixed müllerian tumor (MMMT)), leiomyosarcoma is seldom associated with a history of pelvic radiation.

Gross Findings

Most leiomyosarcomas are intramural, and 50–75% are solitary masses (Schwartz et al. 1993). A higher proportion involves the cervix than is the case with leiomyoma. Leiomyosarcoma

averages 6–9 cm in diameter and is soft or fleshy with poorly defined margins (Abeler et al. 2009), and its cut surface is gray-yellow or pink, often with areas of necrosis and hemorrhage (Fig. 26; 09-1153). All of these characteristics help distinguish it from leiomyoma, which tends to be smaller, firmer, more clearly demarcated and is less likely to be hemorrhagic and necrotic (Table 3). On the other hand, most smooth muscle neoplasms that have a peculiar gross appearance are found to be benign and to exhibit some form of "degeneration," usually ischemic. Benign and malignant smooth muscle neoplasms are not reliably distinguishable by most imaging modalities (Schwartz and Kelly 2006), except for qualitative magnetic resonance (MR) imaging with texture analysis (Lakhman et al. 2017).

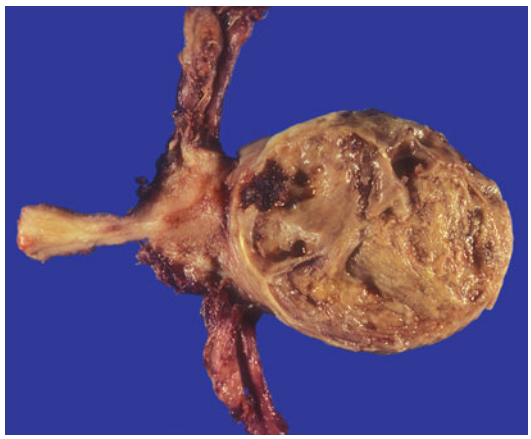

Fig. 26 Typical leiomyosarcoma. A solitary neoplasm, softer than the usual leiomyoma, contains areas of necrosis and hemorrhage on the cut surface

Table 3 Comparison of the gross pathology of leiomyoma and leiomyosarcoma

Leiomyoma	Leiomyosarcoma
Usually multiple	Usually solitary (50–75%)
Variable size, usually 3–5 cm	Large, usually 5–10 cm or larger
Firm, whorled cut surface	Soft, fleshy cut surface
White	Yellow or tan
Hemorrhage and necrosis (infarction type) infrequent	Hemorrhage and necrosis (coagulative tumor cell type) frequent

Microscopic Findings in Conventional Leiomyosarcoma

A typical leiomyosarcoma is composed of fascicles of spindle cells with abundant eosinophilic cytoplasm (Fig. 27), and frequently contains longitudinal cytoplasmic fibrils, best appreciated with a trichrome stain. The nuclei are fusiform, usually have rounded ends, and are hyperchromatic with coarse chromatin and prominent nucleoli (Fig. 28). These tumors often display marked cellular pleomorphism, especially in those that are poorly differentiated (Figs. 29 and 30), and 50% contain multinucleated cells. Leiomyosarcomas occasionally include giant cells resembling osteoclasts (Darby et al. 1975; Marshall et al. 1986; Patai et al. 2006) and, rarely, prominent xanthoma cells

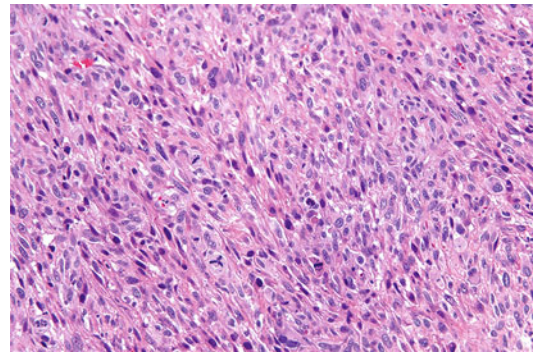

Fig. 27 Leiomyosarcoma. The tumor cells are spindle-shaped with eosinophilic cytoplasm. The nuclei are fusiform, hyperchromatic, and atypical, and there are many mitotic figures

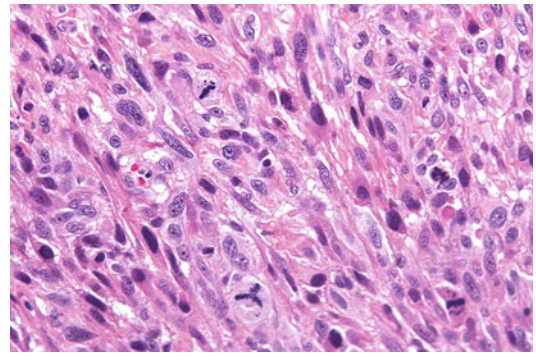

Fig. 28 Leiomyosarcoma. The tumor cells vary in size and shape. Several mitotic figures are present including an abnormal one

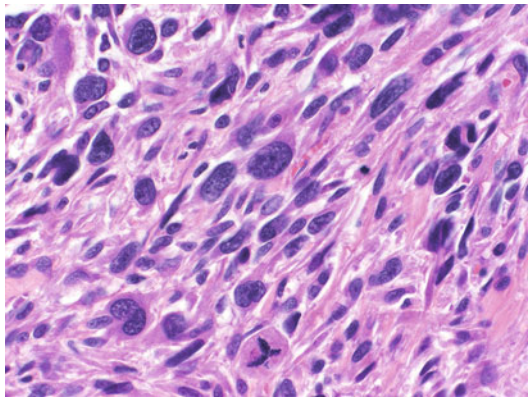

Fig. 29 Leiomyosarcoma. The tumor cell nuclei are pleomorphic, with some giant nuclei and an atypical mitotic figure

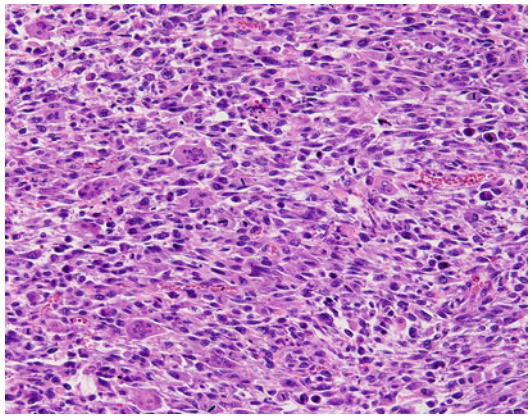

Fig. 30 Leiomyosarcoma with anaplastic features and giant cells. The focus displayed is consistent with leiomyosarcoma, provided it is present in an otherwise typical leiomyosarcoma. Out of context, this focus could be diagnosed as undifferentiated uterine sarcoma, pleomorphic type

Table 4 Histologic criteria for the diagnosis of uterine smooth muscle tumors with standard smooth muscle differentiation

Tumor cell necrosis	Atypia	MF/10 HPF	Diagnosis
Present	Diffuse moderate to severe	Any level	Leiomyosarcoma
Present	None to mild	10 or more	Leiomyosarcoma
Present	None to mild	Less than 10	Smooth muscle tumor of LMP/STUMP[a]
Absent	Diffuse moderate to severe	10 or more	Leiomyosarcoma
Absent	Diffuse moderate to severe	Less than 10	"Smooth muscle tumor with low risk of recurrence" STUMP
Absent	None to mild	Less than 5	Leiomyoma
Absent	None to mild	5 – 20	Mitotically active leiomyoma
Absent	Focal moderate to severe	5 or more	STUMP (limited experience)
Absent	Focal moderate to severe	Less than 5	Leiomyoma with bizarre nuclei

[a]If infarcted/apoplectic leiomyoma is excluded
LMP: low malignant potential; STUMP: smooth muscle tumor of uncertain malignant potential

(Grayson et al. 1998). Many invade the surrounding myometrium, and 10–22% invade the vasculature, but a leiomyosarcoma with a circumscribed margin can give rise to metastases.

The main criteria used to diagnose leiomyosarcoma of the uterus are the presence of nuclear atypia, a high mitotic index (>10 MF/10 HPF but typically >15 MF/10HPF) (Pelmus et al. 2009), and coagulative tumor cell necrosis, though the latter is not essential (Table 4). The differential diagnosis generally includes leiomyoma variants, smooth muscle tumor of uncertain/low malignant potential, endometrial stromal sarcoma (particularly those variants containing spindle cells), IMT, undifferentiated sarcoma, the sarcomatous component of adenosarcoma or carcinosarcoma, malignant solitary fibrous tumor, and extension of gastrointestinal stromal tumor from the rectum. With the exception of carcinosarcoma (see ▶ Chap. 9, "Endometrial Carcinoma") and gastrointestinal stromal tumor (which is CD117, DOG-1, and CD34-positive), these entities are discussed in detail later in this chapter. The remaining entities can be distinguished by morphology, immunophenotype, and assessment for gene fusions.

Microscopic Findings in Myxoid Leiomyosarcoma

Myxoid leiomyosarcoma is a large, gelatinous neoplasm that usually appears circumscribed on gross examination (Kunzel et al. 1993; Schneider et al. 1995) and is becoming a diagnosis of exclusion given the wide differential diagnosis, presented below. Microscopically, the smooth muscle cells are usually widely separated by myxoid material (Fig. 31) (King et al. 1982). The characteristic low cellularity partly accounts for the low mitotic index in most myxoid leiomyosarcomas. Sometimes, however, the mitotic index is high and there is a high degree of atypia. In addition to the myxoid appearance, other microscopic features that help identify the tumor as a leiomyosarcoma include myometrial infiltration and vascular invasion. Infiltrative growth was key to recognition of an unusual myxoid leiomyosarcoma that arose within a leiomyoma (Mittal et al. 2000). Despite the low mitotic counts, myxoid leiomyosarcoma has the same unfavorable prognosis as typical leiomyosarcoma. Myxoid smooth muscle tumors of the uterus must be regarded with suspicion, and any myxoid smooth muscle tumor with significant nuclear atypia, regardless of the mitotic count or the presence or absence of necrosis, should be classified as a leiomyosarcoma.

Proper diagnosis requires distinguishing the myxoid differentiation found in myxoid leiomyosarcomas from the vastly more prevalent hydropic changes seen in degenerating leiomyomas (Clement et al. 1992). In myxoid leiomyosarcoma, not only is the stroma myxoid but the cells are enlarged with hyperchromatic nuclei and pleomorphism is usually obvious. Myxoid leiomyosarcoma usually bears some resemblance to soft tissue myxofibrosarcoma, although the vasculature tends not to be as prominent and the degree of nuclear atypia is frequently lower in myxoid leiomyosarcoma. Myxoid leiomyosarcoma must be differentiated from focal myxoid change (Pugh et al. 2012), inflammatory fibromyxoid tumor (*ALK*-rearranged) (Bennett et al. 2017a; Parra-Herran et al. 2015; Rabban et al. 2005), the sarcomatous component of adenosarcoma, and myxoid/fibromyxoid variants of endometrial stromal sarcoma (Lewis et al. 2017; Oliva et al. 1999; Yilmaz et al. 2002), all discussed subsequently in this chapter.

Microscopic Findings in Epithelioid Leiomyosarcoma

Epithelioid leiomyosarcomas are composed of round or polygonal cells and exhibit one of the patterns of epithelioid differentiation (leiomyoblastoma, clear cell, or plexiform) (Fig. 32). Like myxoid leiomyosarcoma, these tumors should be considered a diagnosis of exclusion based on similarity to many other tumors,

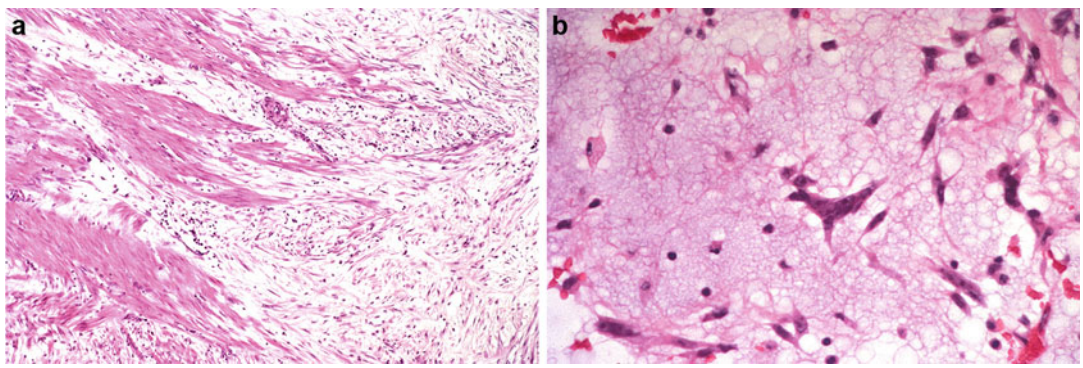

Fig. 31 Myxoid leiomyosarcoma. (**a**) Abundant myxoid stroma widely separates bundles of smooth muscle cells, resulting in a hypocellular appearance. (**b**) The degree of nuclear atypia can be deceptively bland, and because the tumor cells are widely separated by myxoid stroma, mitotic activity is low

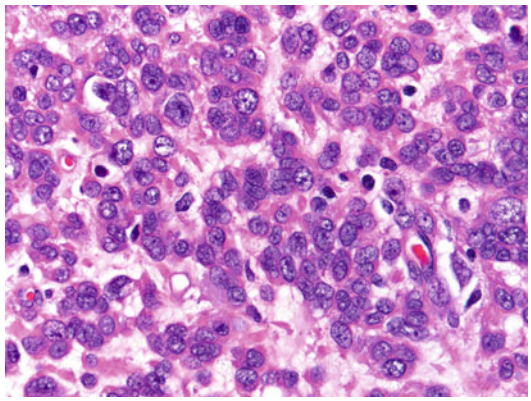

Fig. 32 Epithelioid leiomyosarcoma of the "leiomyoblastoma" type. Tumor cells are polygonal with pale cytoplasm and atypical nuclei. Mitotic figures are not numerous, but coagulative tumor cell necrosis was extensive

discussed below. The leiomyoblastoma pattern is most common, although clear cell epithelioid leiomyosarcomas have also been reported (Prayson et al. 1997; Silva et al. 1995, 2004). These tumors are distinguished from other epithelioid smooth muscle tumors by the usual features of malignancy: significant nuclear atypia and either necrosis or > 5 MF/10 HPF qualify a tumor as leiomyosarcoma (Atkins et al. 2001; Clement 2000; Kempson and Hendrickson 2000; Kurman and Norris 1976; Moinfar et al. 2007; Prayson et al. 1997). The differential diagnosis of epithelioid leiomyosarcoma includes leiomyoma variants, smooth muscle tumor of uncertain/low malignant potential, PEComa, carcinoma, metastatic melanoma (S-100 positive), placental site and epithelioid trophoblastic tumors (GATA-3 positive), ASPS (HMB-45 negative with *Xp11* translocation), and endometrial stromal tumors, as some have an epithelioid appearance (Lee et al. 2012b). With the exception of carcinoma (discussed in ▶ Chap. 9, "Endometrial Carcinoma"), placental site trophoblastic tumor (discussed in ▶ Chap. 20, "Gestational Trophoblastic Tumors and Related Tumorlike Lesions"), and melanoma, these entities are discussed in detail later in this chapter.

Otherwise conventional smooth muscle tumors with low mitotic counts, on rare occasions, prove to be clinically malignant. Unless the tumor is invasive or contains abnormal mitotic figures or areas of tumor cell necrosis, there are no good grounds for suspecting that it is a leiomyosarcoma until it announces itself by metastasizing.

Immunohistochemistry

Immunohistochemistry is generally not required for the diagnosis of leiomyosarcoma, but immunostains are occasionally necessary to differentiate it from other uterine malignancies such as undifferentiated endometrial sarcoma or sarcomatoid carcinoma. Immunostains using a variety of antibodies can confirm that extrauterine sarcoma deposits show smooth muscle differentiation and hence are compatible with metastatic leiomyosarcoma. Smooth muscle actin, desmin, and caldesmon are the best established markers, but calponin and smooth muscle myosin are also occasionally used for this purpose; all of these stain the cytoplasm. Because myofibroblasts can also stain with smooth muscle markers, particularly smooth muscle actin, positive staining with one of these markers is not conclusive evidence of smooth muscle differentiation. Distinction from endometrial stromal tumors requires close attention, as leiomyosarcoma often stains positive for the stromal marker CD10. In one study, eight of nine leiomyosarcomas were CD10-positive (low to moderate intensity, staining in 5–60% of tumor cells) (Oliva et al. 2002b). However, CD10 staining in smooth muscle tumors is generally weak and focal (McCluggage et al. 2001b; Toki et al. 2002). Myometrial smooth muscle cells are frequently immunoreactive for cytokeratin, so leiomyosarcomas occasionally show positive cytoplasmic staining for cytokeratin (Oliva et al. 2002b).

Many investigators have proposed immunohistochemical stains that could distinguish between benign and malignant smooth muscle tumors, but markers such as p53 (Fig. 33), p16 (Fig. 34), mib-1, ER, and progesterone receptor are variably expressed in leiomyomas and leiomyosarcomas, limiting their

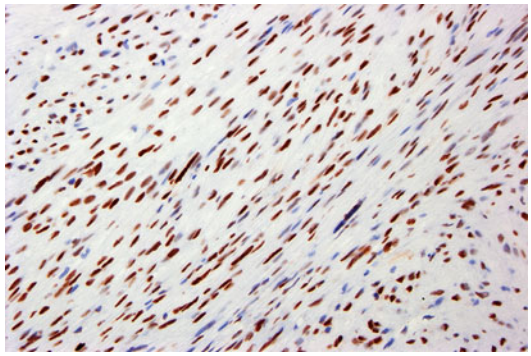

Fig. 33 Positive staining for p53 in leiomyosarcoma

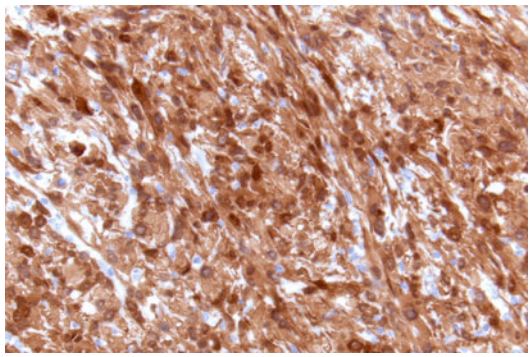

Fig. 34 Positive staining for p16 in leiomyosarcoma

utility in differential diagnosis (Amada et al. 1995; Atkins et al. 2008; Blom and Guerrieri 1999; Bodner et al. 2004; Bodner-Adler et al. 2005; Chen and Yang 2008; de Vos et al. 1994; Gannon et al. 2008; Hall et al. 1997; Layfield et al. 2000; Leiser et al. 2006; Leitao et al. 2004; Mittal and Demopoulos 2001; O'Neill et al. 2007; Watanabe and Suzuki 2006; Zhai et al. 1999). For example, although mutation of the *p53* gene or positive staining for p53 (strong nuclear staining in >50% of tumor cell nuclei) is observed mainly in leiomyosarcomas, albeit in a minority (Gannon et al. 2008; O'Neill et al. 2007), leiomyomas with bizarre nuclei and smooth muscle tumors of low malignant potential (SM-LMP)/STUMP have been reported to stain with the same frequency and intensity as leiomyosarcoma (Chen and Yang 2008). The greatest overlap in immunophenotype is between usual leiomyosarcoma and leiomyomas with bizarre nuclei.

A summary of antibodies that can be used in the differential diagnosis of usual, myxoid, and epithelioid leiomyosarcomas is found in Tables 5, 6, and 7.

Molecular Pathology

Comparison of gene expression profiles in uterine leiomyosarcoma and normal myometrium has revealed differences in cell cycle regulation, DNA repair, and genomic integrity (Barlin et al. 2015). Gene expression profiling can also differentiate primary uterine leiomyosarcoma from leiomyosarcoma metastases (Davidson et al. 2014) and aggressive from more indolent tumors. In one study, unsupervised clustering of leiomyosarcomas identified two clades (genomic subgroups) that were reproducibly associated with significant differences in progression-free and overall survival (Barlin et al. 2015). Interpreting work performed by the Cancer Genome Atlas initiative (TCGA), van de Rijn and colleagues identified three genomic categories of leiomyosarcoma, one that was highly enriched for uterine tumors and two that were shared between uterine and soft tissue leiomyosarcomas (Guo et al. 2015). One of the latter subtypes was associated with poor prognosis. The subtypes differed significantly in expression levels for genes for which novel targeted therapies are being developed, suggesting that different leiomyosarcoma subtypes may respond differentially to targeted therapies (Guo et al. 2015).

The most frequently mutated genes in uterine leiomyosarcoma are *TP53* (in one-third of cases), *alpha thalassemia/mental retardation syndrome X-linked* (*ATRX*; in one-quarter of cases), and *mediator complex subunit 12* (*MED12*; in one-fifth of cases) (Makinen et al. 2016). Loss of ATRX expression is associated with alternative lengthening of telomeres (ALT), leading to acquisition of an "ALT phenotype," which may be therapeutically targeted (Makinen et al. 2016). The presence of *MED12* mutations in both leiomyomas and leiomyosarcomas has led to speculation that some leiomyosarcomas may

Table 5 Immunohistochemical features of conventional (spindle) leiomyosarcoma and entities in the differential diagnosis

	Des	CD10	p53	MIB-1	FH	C-kit	STAT6
LMS	++	–/+	–/++	Diffuse	Intact	Variable	–
LMA-apo	++	–/+	NA	Geographic	Intact	NA	–
LMA-bizarre (1)	++	–/+	–	Low	Lost	NA	–
LMA-bizarre (2)	++	–/+	++/–	Variable	Intact	NA	–
ESS-LG	–/+	++/–	–	Low	Intact	Variable	–
GIST	–	–/+	–/+	Variable	NA	Diffuse	–
SFT	–	+/–	–	Variable	NA	–	++
Sarcoma-het	–*	–/+	++	Diffuse	NA	Variable	–
Sarcoma-undiff	–	–/+	++	Diffuse	NA	Variable	–

Des: desmin; FH: fumarate hydratase; LMS: leiomyosarcoma; LMA: leiomyoma; apo: apoplectic; ESS-LG: low-grade endometrial stromal sarcoma; GIST: gastrointestinal stromal tumor; SFT: deficient solitary fibrous tumor; het: heterologous; undiff: undifferentiated bizarre; NA: not analyzed in literature; LMA-bizarre (1): FH-deficicat bizarre leiomyoma; LMA-bizarre (2): *p53* – mutated bizarte leiomyoma
*Except in rhabdomyosarcoma

Table 6 Immunohistochemical features of myxoid leiomyosarcoma and entities in the differential diagnosis

	Des	SMA	ALK	CD10	Cycl D1	BCOR	Ker
LMS-myx	+/–	+/–	–	–	–	–	–
LMA-degen	++	++	–	–	–	–	–
IMT	+/–	+/–	++	+/–	–	–	–/+
ESS-myx	–	+/–	–	+	–	–/+	–
ESS-BCOR	+/–	+/–	–	+	+/–	+/–	–
Carcinoma-undiff[a]	–	–	–	–	+/–	–	+/–
Sarcoma-undiff	–	–/+	–	–/+	–/+	–	–

Des: desmin; SMA: smooth muscle actin; Ker: cytokeratin; LMS: leiomyosarcoma; myx: myxoid; LMA: leiomyoma; degen: degenerative; IMT: inflammatory myofibroblastic tumor; ESS: endometrial stromal sarcoma; undiff: undifferentiated
[a]These carcinomas are also typified by loss of PAX-8 and e-cadherin expression, DNA mismatch repair deficiency, and abnormalities in chromatin remodeling (i.e., ARID1A, SMARCB1, or SMARCA4 expression loss)

Table 7 Immunohistochemical features of epithelioid leiomyosarcoma and entities in the differential diagnosis

	Des	HMB45	TFE3	CD10	Inh	Cycl D1	Ker	hPL
LMS-epi	++/–	–/+	–	–/+	–	–	–/+	–
PEComa (1)	+/–	+	–	–/+	–	–	–	NA
PEComa (2)	–	++	++	NA	–	–	–	NA
ESS-sex cord	+/–	–	–	++	++	–	+/–	NA
ESS-YWHAE (LG)	–	–	–	++	–	–	–	NA
ESS-YWHAE (HG)	–	–	–	–	–	++	–	NA
UTROSCT	+/–	–	–	+	++	–	+/–	NA
Carcinoma-undiff	–	–	–	–	–	–/+	+/–	NA
PSTT	–	–	–	+/–	+	–	++	+
Sarcoma-undiff	–	–	–	–/+	–	–/+	–	NA

Des: desmin; Inh: inhibin; Ker: cytokeratin; hPL: human placental lactogen; LMS: leiomyosarcoma; PEComa (1): perivascular epithelioid cell tumor with epithelioid eosinophilic cells; PEComa (2): perivascular epithelioid cell tumor with clear cells, resembling *Xp11*-translocated renal cell carcinomas; ESS: endometrial stromal sarcoma; YWHAE: *YWHAE* translocation present; LG: low grade; HG: high grade; UTROSCT: uterine tumor resembling ovarian sex cord tumor; undiff: undifferentiated; PSTT: placental site trophoblastic tumor; NA: not analyzed in literature

arise from a preexisting leiomyoma (Bertsch et al. 2014; Makinen et al. 2016; Matsubara et al. 2013). Rare myxoid leiomyosarcomas harbor translocations involving *PLAG1* (Arias-Stella et al. 2018). In a study that assessed clinical outcomes in uterine and extrauterine leiomyosarcomas by mutated genes (Yang et al. 2015), almost all *TP53*-mutated leiomyosarcomas were located in the uterus or retroperitoneum. *ATRX* mutations were associated with poor differentiation, the presence of tumor necrosis, and worse overall survival.

In contrast to knowledge about gene mutations in leiomyosarcomas, the literature regarding epigenetic changes and posttranscriptional regulation of gene expression is limited. One study identified 94 micro-RNAs (miRNAs) that were significantly differentially expressed in endometrial stromal sarcoma and leiomyosarcoma, 18 of which were overexpressed in leiomyosarcoma, as well as a miRNA signature distinguishing primary from metastatic leiomyosarcoma (Ravid et al. 2016).

Clinical Behavior and Treatment

A clinicopathologic portrait of leiomyosarcoma as currently defined is provided by a retrospective review of uterine leiomyosarcomas treated at the Mayo Clinic (Giuntoli et al. 2003). Disease was confined to the uterus in 68% of the 208 patients, while 6% had cervical involvement; approximately half of these had cervical involvement only. Nine percent were stage III and 20% stage IV according to the International Federation of Gynecology and Obstetrics (FIGO) system, meaning that they had invaded abdominal tissues (Table 2) (Prat 2009).

Leiomyosarcoma is a highly malignant neoplasm with poor survival rates when tumors are classified using contemporary criteria. Overall 5-year survival rates in series using these criteria range from 15% to 35% (Blom et al. 1998; Larson et al. 1990; Pelmus et al. 2009); variation results from differences in how those criteria are interpreted and applied. When only stage I and II tumors are considered, the 5-year survival rate is 40–70% (Blom and Guerrieri 1999; Gadducci et al. 1996a; Larson et al. 1990; Mayerhofer et al. 1999; Nola et al. 1996; Nordal et al. 1995; Pautier et al. 2000; Pelmus et al. 2009; Wolfson et al. 1994), and 3-year progression-free survival is about 30%, according to a Gynecologic Oncology Group (GOG) series of 59 cases (Major et al. 1993).

Prognostic Prediction and Clinical Outcomes

The prognosis of leiomyosarcoma depends chiefly on its anatomical extent, often categorized as stage. For stage I tumors (confined to the uterus), some investigators have found the size of the neoplasm to be an important prognostic factor (Abeler et al. 2009). In one series, all patients with tumors larger than 5 cm died of disease, compared to only three of eight patients with tumors smaller than 5 cm (Evans et al. 1988). In another series of metastasizing leiomyosarcomas, only 20% were less than 5 cm (Jones and Norris 1995). Whether premenopausal status is linked with more favorable outcomes remains unclear. Mitotic index also appears to be a prognostic indicator; several series confirm this, including the large GOG study of early-stage leiomyosarcoma (Abeler et al. 2009; Gadducci et al. 1996a; Larson et al. 1990; Major et al. 1993; Pautier et al. 2000; Pelmus et al. 2009), while only one study found otherwise (Evans et al. 1988). PR expression may also be prognostically favorable in stage I leiomyosarcoma (Leitao et al. 2012), while myxoid or epithelioid differentiation and diffuse, severe nuclear atypia may be unfavorable (Wang et al. 2011).

The nomogram created based on data from 270 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) weighs prognostic factors differently (Zivanovic et al. 2012). Median overall survival within this cohort was only 3.75 years. The nomogram's power (https://www.mskcc.org/nomograms/uterine) in predicting postresection 5-year overall survival was validated externally (Iasonos et al. 2013). These analyses indicate that the most important staging distinction is between uterus-confined disease and extrauterine disease; much less important is assessment of cervical involvement and tumor size. Listed in order of decreasing importance, the categorical (noncontinuous) predictive variables included "tumor grade" (which was not

clearly defined), loco-regional metastasis, distant metastasis, and cervical involvement. The continuous variables included mitotic index, tumor size (cm), and age at diagnosis. Notably absent from the list is FIGO stage; both FIGO and American Joint Commission on Cancer (AJCC) staging for leiomyosarcomas have been criticized (Raut et al. 2009; Zivanovic et al. 2009).

Uncontained morcellation of a leiomyosarcoma, performed either manually or with a power morcellator, has a significantly negative impact on survival because of subsequent peritoneal spread. A preliminary study performed years before the current debate about the risks and benefits of morcellation demonstrated a statistically nonsignificant increase in the rate of pelvic dissemination following this procedure (Morice et al. 2003). Almost 10 years later, uncontained morcellation was conclusively shown to not only significantly increase the risk of abdomino-pelvic recurrence of leiomyosarcoma, as 64.3% of patients developed disseminated disease, but also to shorten survival (Park et al. 2011; Seidman et al. 2012).

Peritoneal recurrence following morcellation is not limited to leiomyosarcomas, as it also occurs with SM-LMP/STUMPs, endometrial stromal sarcoma, and leiomyoma as well (Tulandi et al. 2016). Nonetheless, morcellation has only been conclusively shown to impair survival in leiomyosarcoma (Seidman et al. 2012). Patients with morcellated leiomyosarcomas should therefore be offered surgical reexploration to detect peritoneal dissemination (Oduyebo et al. 2014).

As no universally agreed-upon grading scheme for leiomyosarcoma exists, pathologists should instead comment on maximum tumor diameter, mitotic index, the presence or absence of necrosis and its extent if present, the nature of the tumor periphery (invasive or circumscribed) presence of morcellation and the presence or absence of vascular space involvement.

Metastasis and Recurrence

The frequency of lymph node metastasis varies from series to series but is substantially lower than that found in clinical stage I and II high-risk endometrial carcinomas (Giuntoli et al. 2003). In a GOG study, 2 of 59 patients (3%) had lymph node involvement, 2 had adnexal involvement, and 1 had positive peritoneal cytology (Major et al. 1993). Another study of 108 patients from MSKCC, 14% of whom underwent lymph node sampling, found lymph node involvement in 8% of patients, all of whom had gross extrauterine disease and obviously enlarged lymph nodes (Leitao et al. 2003). Moreover, a high percentage of lymph node-negative patients experienced recurrence or died of disease. In view of this, lymph node sampling at initial surgery does not appear worthwhile in this disease. Nonetheless, as many as 44% of patients who die from leiomyosarcoma have lymph node metastasis at autopsy (Fleming et al. 1984; Rose et al. 1989).

Leiomyosarcoma relapses occur both locally-regionally and hematogenously; the following locations were the sole site of relapse: vagina 22%, pelvis 19%, lung 22%, bone 9%, and retroperitoneum 12%. Relapse in both lung and pelvis occurred in 16% of patients (Giuntoli et al. 2003). In another study, the first recurrence was in the pelvis in 14% of cases and in the lung in 41% (Major et al. 1993).

Criticism/Value of Tumor Grading

At least 75–90% of leiomyosarcomas defined by Stanford criteria are histologically high grade, and clinical outcome data indicate that such tumors are highly malignant. In a Mayo Clinic study (Giuntoli et al. 2003), leiomyosarcomas assigned grades 2, 3, or 4 had nearly identical survival curves. Similarly, a grading scheme designed for soft tissue neoplasms has been shown to have no prognostic significance for uterine sarcomas (Pautier et al. 2000; Pelmus et al. 2009). It is therefore inappropriate to assign either a numerical grade (i.e., grade 2 of 3 or 4) or a qualitative grade based on degree of differentiation (i.e., well differentiated) to uterine leiomyosarcoma; all leiomyosarcomas that meet Stanford criteria for leiomyosarcoma should be considered intrinsically high grade.

Nonetheless, some uterine smooth muscle tumors have the potential to metastasize after long disease-free intervals and follow an indolent course. Such tumors appear to be a subset of

leiomyoma variants, sometimes termed "atypical leiomyomas." In a Mayo Clinic study, 3 of 18 patients with leiomyoma variants died of disease, but between 6 and 11 years after diagnosis; in contrast, almost all patients whose lethal tumors met Stanford criteria for leiomyosarcoma died within 5 years of diagnosis (Giuntoli et al. 2007). The 18 patients with leiomyoma variants were originally considered to have "low-grade leiomyosarcoma," but labeling all patients as such would potentially have left them vulnerable to unnecessary chemo- and radiotherapy (Giuntoli et al. 2003). Furthermore, there is no evidence that any type of adjuvant therapy changes the clinical course of potentially recurring atypical smooth muscle tumors that fail to meet Stanford criteria for leiomyosarcoma. Similarly, a study from MSKCC found that patients with recurrent atypical leiomyomas, some of which were leiomyomas with bizarre nuclei, experienced disease progression at a mean time of 12 years, and none died of disease (Veras et al. 2011). This study also highlighted the significant heterogeneity of the group of tumors historically considered to be "low-grade leiomyosarcomas," which comprised usual leiomyosarcomas (the clinical outcomes of which were similar to usual leiomyosarcomas that were considered "high grade"), leiomyoma variants and endometrial stromal neoplasms with spindle cells. Whether it is reasonable to use the term "low-grade leiomyosarcoma" for recurrent, histologically low-grade smooth muscle tumors is discussed in the STUMP portion of this chapter.

Treatment

For postmenopausal women, primary therapy for early-stage leiomyosarcoma is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Whether oophorectomy is warranted in premenopausal women is more controversial. The ovaries are the site of metastatic disease in clinically low-stage leiomyosarcoma in only 2–3% of cases (Leitao et al. 2003; Major et al. 1993). While some studies indicate that oophorectomy does not influence outcomes (Gard et al. 1999; Giuntoli et al. 2003; Larson et al. 1990), another reported that patients with so-called low-grade smooth muscle neoplasms metastatic to the lung responded to oophorectomy alone (Abu-Rustum et al. 1997). However, these patients' leiomyosarcomas may not have met Stanford criteria, which suggest that patients with recurrent STUMPs and metastasizing leiomyomas may benefit from this procedure. Similarly, aromatase inhibitors are a suitable option for postmenopausal patients with ER/PR-positive, small volume, and/or slowly progressive disease, where neither resection nor cytotoxic chemotherapy is warranted (Hyman et al. 2014). Therefore, while there may be theoretical benefit to the hormonal ablation afforded by oophorectomy in patients whose tumors express ER and PR, there is no compelling need to perform oophorectomy to detect occult metastasis.

The literature provides conflicting reports on the efficacy of radiotherapy and chemotherapy in the management of leiomyosarcoma (Gadducci et al. 1996a, 2008; Giuntoli and Bristow 2004; Giuntoli et al. 2003; Hensley et al. 2002; Mayerhofer et al. 1999; Sutton et al. 2005; Zivanovic et al. 2009). Adjuvant pelvic radiotherapy was previously used under the assumption that it might decrease the likelihood of pelvic recurrence. Postoperative pelvic radiation therapy is no longer advocated as a standard treatment since a prospective, randomized trial reported no benefit to overall or recurrence-free survival (O'Cearbhaill and Hensley 2010; Reed et al. 2008). Pelvic radiotherapy may still be considered in highly selected cases, such as for patients with local relapse or residual disease following surgery. For patients with resected stage I uterine leiomyosarcoma, neither radiation therapy nor chemotherapy has been conclusively demonstrated to be effective, and both are associated with significant toxicities. Thus, there is a strong argument in favor of "watching and waiting" (i.e., withholding therapy until disease progression) in early-stage cases (Hensley 2017; Littell et al. 2017).

The combination of gemcitabine and docetaxel is considered a good first-line therapy in patients with disseminated disease (Hyman et al. 2014). Reported response rates are 27–53% with median progression-free survivals that range from 4.4 to 5.6 months (Hensley et al. 2002, 2008a, b); these results are disappointing for individual patients,

but they clearly outperform previous chemotherapeutic regimens. Among targeted agents, only the multi-tyrosine kinase inhibitor pazopanib has been approved for any soft tissue sarcoma, and the Aurora A kinase inhibitor is in trials based on strong preclinical evidence (Hyman et al. 2014). Hormonal agents are discussed above.

Smooth Muscle Tumor of Uncertain/ Low Malignant Potential

"Smooth muscle tumor of uncertain malignant potential" (STUMP) is a term generally applied to smooth muscle tumors when there is uncertainty about diagnostic criteria for malignancy (i.e., is the necrosis of coagulative type?) (Fig. 35), the type of smooth muscle differentiation present (i.e., is the tumor truly epithelioid?), and malignant potential (i.e., scarcity of clinical outcomes data). The term may also be applied to tumors with a low risk of recurrence. Artificially separating the "uncertain" entities from the "possibly recurring" entities would create two categories: STUMP and smooth muscle tumor of low malignant potential (SM-LMP). These terms are both controversial, although the "STUMP" term is widely understood by pathologists and clinicians. Furthermore, "lumpers" (as opposed to "splitters") may argue that by expressing uncertainty about a given tumor's malignant potential, one also implies an ill-defined risk of clinically malignant behavior.

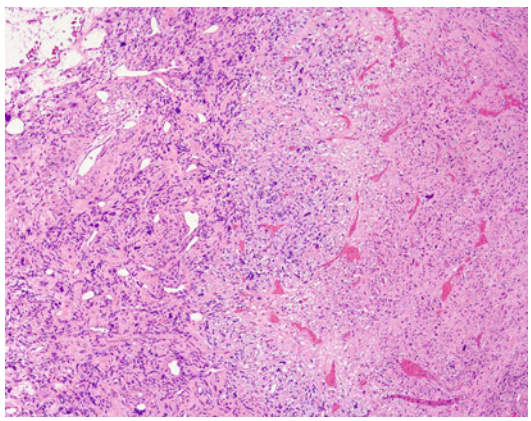

Fig. 35 STUMP. This atypical smooth muscle tumor contains several areas of necrosis that are indeterminate for coagulative tumor cell necrosis. The background resembles a leiomyoma with bizarre nuclei, with a mitotic index of 5–7 MF/10HPF. This zone of necrosis most closely resembles infarct-type necrosis, with loss of reticulin, but the proliferative rate using mib-1 was lowest in areas surrounding the infarct, a feature that has been suggested to support coagulative tumor cell necrosis

Regardless of the term used, it is very important to note that **none** of the following tumor types should be considered STUMPs or SM-LMPs despite the fact that some may recur locally, can be intravascular, and/or involve broad ligament, other pelvic soft tissues, peritoneum, and lung. These include mitotically active leiomyoma, cellular leiomyoma, apoplectic leiomyoma, leiomyoma with bizarre nuclei, diffuse leiomyomatosis, dissecting leiomyoma, metastasizing leiomyoma, IVL, DPL, IMT, endometrial stromal neoplasia with smooth muscle differentiation, and peritoneal implantation of morcellated leiomyoma. To further avoid contamination of the STUMP/SM-LMP category, one must be sure to extensively sample any smooth muscle tumor demonstrating at least one criterion for malignancy. Recurrence or metastasis of the aforementioned leiomyoma variants has historically been considered "benign" provided that the histology of the recurrence or metastasis retains the appearance of the preceding leiomyoma. These secondary tumors can be treated successfully by surgical excision, with or without hormonal agents.

Some leiomyomas with bizarre nuclei and smooth muscle tumors described by the Stanford group as "atypical leiomyoma with low risk of recurrence" fall within the STUMP/SM-LMP category (Bertsch et al. 2014). Since most such tumors with mitotic indices of less than 5 MF/10 HPF follow a benign or at most locally recurring clinical course, it is reasonable to continue to categorize these tumors as leiomyoma variants provided they are very well sampled. Those with higher mitotic indices (5–10 MF/10HPF) may be classified as either SM-LMPs or as "atypical leiomyomas with recurring potential/low risk of recurrence."

Therefore, after excluding leiomyoma variants and leiomyosarcoma, the STUMP category contains three clinical entities: (1) benign smooth muscle tumors that are difficult to diagnose; (2) potentially recurring smooth muscle tumors with indolent recurrence and/or long disease-free intervals (SM-LMPs); and (3) conventional leiomyosarcoma that is difficult to diagnose. No tools are yet able to distinguish between the first and second entities, but use of some of the immunohistochemical and microscopic approaches discussed subsequently may be diagnostically useful for the third set of tumors, though they have limitations.

In addition to benign-appearing recurrences of leiomyomas and leiomyoma variants in extraperitoneal sites, some recurrences and metastases following a leiomyoma diagnosis may show evidence of morphologic evolution. Recurrent/metastatic leiomyomas that meet criteria for leiomyosarcoma should be categorized as such, but recurrent/metastatic tumors that are more cellular, more mitotically active, or are invasive beyond that of a typical leiomyoma, while falling short of a leiomyosarcoma diagnosis using Stanford criteria, should be categorized as STUMP or "SM-LMP." The term "low-grade leiomyosarcoma" may be considered for such cases, especially since many clinicians will have difficulty understanding the concept of a recurrent/metastatic atypical smooth muscle neoplasm, but there is no firm precedent for this term in the gynecologic pathology literature. Regardless of the term used, it is crucial to convey that **such recurrent histologically low-grade tumors do not constitute conventional uterine leiomyosarcoma**, as they are treated by entirely different approaches.

Microscopic Findings

Careful microscopic examination aids in distinguishing STUMP from usual leiomyosarcoma. This differential diagnosis is particularly problematic when there is uncertainty about the mitotic index, which would affect predictions of the tumor's clinical behavior. This situation most frequently occurs in smooth muscle neoplasms with standard smooth muscle differentiation that lack tumor cell necrosis, have moderate to severe atypia, and have a mitotic index that falls just short of 10 MF/10 HPF. The diagnosis of STUMP in this situation is treacherous and is potentially misleading, as classifying a tumor with diffusely distributed atypical nuclei and 9 MF/10 HPF as "smooth muscle tumor with low risk of recurrence" or STUMP may significantly underestimate the tumor's metastatic potential. Excluding the diagnosis of conventional leiomyosarcoma by extremely thorough sampling to uncover a focus of high mitotic activity in such a tumor is critical.

Immunohistochemistry and Molecular Pathology

Two strategies, immunohistochemistry and molecular analysis, including comparative genomic hybridization (CGH), have been proposed to separate STUMPs from usual leiomyosarcoma and to distinguish between "benign" and potentially malignant STUMPs immunohistochemistry and molecular analysis, including CGH. In addition to phosphohistone immunohistochemistry for accurate mitotic counting and prognostication (Chow et al. 2017; Veras et al. 2009), possibly useful markers include p53 and p16 (Ip et al. 2009; O'Neill et al. 2007). However, these should not be applied when the tumor has the appearance of a leiomyoma with bizarre nuclei, since many of these tumors harbor *p53* mutations that lead to overexpression (Bennett et al. 2017b; Chen and Yang 2008; Ubago et al. 2016; Zhang et al. 2017). Similarities among leiomyomas with bizarre nuclei, STUMPs, and leiomyosarcoma include miRNA expression patterns and rates of *PTEN* deletions (Zhang et al. 2014).

Although p53 and p16 would not distinguish between leiomyomas with bizarre nuclei and leiomyosarcoma, these markers might help to separate conventional leiomyosarcomas from STUMPs lacking "symplastic" features. Perhaps more informative is immunohistochemistry for

ATRX, DAXX, and MED12. Expression of ATRX and DAXX is known to be lost in a subset of leiomyosarcoma (Slatter et al. 2015) and was associated with death due to disease or recurrence in six of six patients with "aggressive" STUMPs and almost all aggressive leiomyosarcomas. These markers likely help determine which STUMPs are actually leiomyosarcomas, although expression of these markers remains unexamined in leiomyomas with bizarre nuclei. Retained expression of these markers is not diagnostically informative, however. Similarly, MED12 expression decreases on a gradient from leiomyoma to STUMP to leiomyosarcoma (Croce and Chibon 2015).While *MED12* mutations are much more frequently found in usual and mitotically active leiomyomas, as stated previously, inhibition of MED12 expression may correlate with malignancy (Pérot et al. 2012).

Finally, it has been proposed that CGH can be used to calculate a "genomic index" score that separates nonrecurring STUMPs from those with recurrences and unfavorable clinical outcomes (Croce et al. 2015). Similar to other approaches, this technique appears to uncover conventional leiomyosarcomas masquerading as STUMPs. As all reported recurrences were documented within 5 years of diagnosis, this technique may not be helpful in the identification of STUMPs prone to late recurrence.

Clinical Behavior and Treatment

STUMP progresses slowly, if at all, and in the small proportion of cases in which it recurs, most affected patients survive. In the largest study on STUMPs to date, among 41 patients with a mean follow-up time of 45 months, recurrence was observed in 3 patients (7.3%; one as leiomyosarcoma and two as STUMP). Recurrence rates were similar for women who underwent myomectomy or hysterectomy. All three patients were alive and disease-free at a mean follow-up time of 121 months (Guntupalli et al. 2009). A prior series of 15 STUMP also found a high survival rate and slow progression when recurrence became evident (Peters et al. 1994). Although necrosis was not recorded, at least some of the tumors in the latter study would qualify as atypical leiomyomas using the Bell et al. criteria. Similarly, Ip and colleagues reported two recurrences out of 16 patients following a diagnosis of "atypical leiomyoma with limited experience," "SM-LMP," "atypical leiomyoma," or "mitotically active leiomyoma, limited experience" (Ip et al. 2009). The two patients who experienced recurrence had been diagnosed with "atypical leiomyoma with limited experience" and both had diffuse immunoreactivity for p53 and p16. Finally, STUMPs may recur in intraperitoneal sites if they are subjected to morcellation (Bogani et al. 2016; Seidman et al. 2012).

In summary, multiple studies since the introduction of the term STUMP have shown that the behavior of these tumors is not "uncertain." The majority of them are benign and only a small percentage recur, which has led some investigators to prefer the designation "SM-LMP" or "smooth muscle tumor with low risk of recurrence" in order to avoid unnecessary adjuvant treatment and to reassure the patient that her fate is not "uncertain."

PEComa and Related Lesions

PEComa is a neoplasm composed of cells showing "perivascular epithelioid cell" (PEC) differentiation (Folpe et al. 2005; Vang and Kempson 2002), although non-neoplastic equivalents are not recognized. Vang and Kempson described two types of uterine PEComas: (1) clear-to-eosinophilic tumor cells with variable staining for smooth muscle and melanocytic markers (Group B PEComa) (Martignoni et al. 2008) and (2) clear tumor cells arranged in nests with strong labeling for HMB-45, but significantly less staining for smooth muscle markers (Group A PEComa) (Vang and Kempson 2002). The PEC family of tumors also includes angiomyolipoma, lymphangiomyomatosis (LAM), and clear cell tumors of the lung and pancreas.

AML is a benign tumor that contains abnormal blood vessels, fat and spindled or epithelioid smooth muscle cells in varying proportions. LAM is generally a microscopic finding in the uterus and consists of dilated lymphovascular spaces associated with smooth muscle cells with flocculent eosinophilic cytoplasm. Pulmonary, uterine, and retroperitoneal nodal LAM may be associated with tuberous sclerosis. In such cases, LAM may be multifocal, invade the myometrium in a tongue-like fashion, and display a paucity of lymphatic vessels. Uterine LAM can also present in sporadic settings, where tongue-like growth is less prevalent and lymphatic vessels more prominent (Hayashi et al. 2011).

Uterine PEComas differ significantly from those that arise in other locations. Among the peculiar attributes of group B uterine PEComas, (1) uterine PEComas more frequently meet criteria for malignancy; (2) malignant PEComas often harbor mutations matching those of uterine leiomyosarcoma and lack those typical of most PEComas (unpublished observations); and (3) hybrid smooth muscle/PEComas occur.

Clinical Features and Gross Findings

PEComas are neoplasms of adulthood, and when they involve the uterus, they typically present either as a mass or cause uterine bleeding. They may be associated with LAM and tuberous sclerosis. PEComas are usually solitary neoplasms ranging in size from 0.5 to 16.0 cm, although rarely multiple lesions are described.

Microscopic Findings

Microscopically, the low-power impression is of either a compressive or, less commonly, an infiltrative neoplasm with a nondistinctive texture and coloration. Sometimes there is a tongue-like pattern of invasion of the myometrium reminiscent of the type of invasion seen in low-grade endometrial stromal sarcoma (Fig. 36) (Vang and Kempson 2002). The pathology of gynecologic PEComas has been reviewed recently (Conlon et al. 2015).

The more common Group B PEComas feature tumor cells that range from predominantly epithelioid to occasionally spindled with moderate to abundant clear-to-eosinophilic cytoplasm with well-defined cell borders (Fig. 37). The tumor cell cytoplasm sometimes has a distinctive granular or finely vacuolated bubbly appearance. The degree of nuclear atypia and the mitotic index are low and necrosis is uncommon, but tumors with significant atypia and frequent mitotic figures occur. A variant with abundant hyalinized stroma that can partially obscure the tumor cells has been reported (Hornick and Fletcher 2008). In addition to the classically described architectural and cytoplasmic characteristics, features that are typical, but not diagnostic of PEComa, include limited smooth muscle marker expression (particularly desmin), striking nuclear atypia with only very few mitotic figures, and metastasis to lymph nodes.

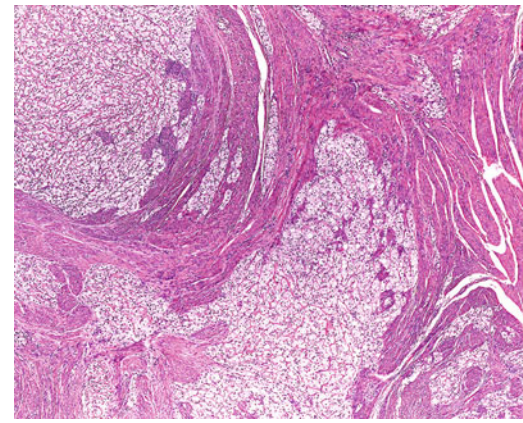

Fig. 36 PEComa (group B). In this uterine PEComa, rounded protrusions of tumor infiltrate the myometrium in a pattern that is somewhat reminiscent of an endometrial stromal sarcoma

The less common Group A PEComas exhibit a nested growth pattern characterized by clustered or alveolar aggregates of clear cells partially encircled by either thin-walled vessels or delicate collagenous stroma (Fig. 38) (Schoolmeester et al. 2015). About one-half of cases have mildly atypical nuclei while others show a range of nuclear atypia, including rare overtly pleomorphic cases. Almost all cases display myometrial invasion, whether permeative, infiltrative, or pushing. Occasional cases have necrosis, lymphovascular invasion, or scarce melanin pigmentation. These cases bear a striking resemblance, including

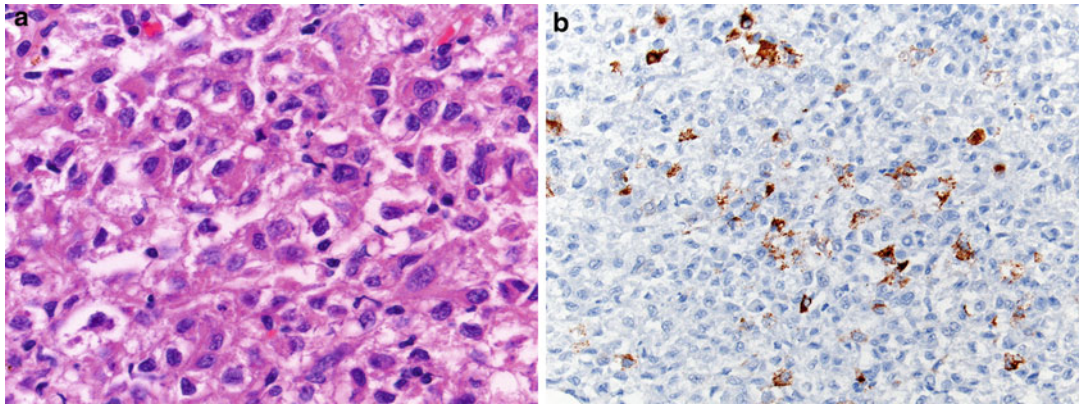

Fig. 37 PEComa (group B). (**a**) The tumor is composed of nests and sheets of epithelioid tumor cells with flocculant eosinophilic cytoplasm and vesicular nuclei with coarse chromatin and conspicuous nucleoli. (**b**) Positive staining for HMB-45 in a uterine PEComa (group B). Staining is typically patchy and often of medium intensity

genomic and immunohistochemical features, to *Xp11*-translocated renal cell carcinomas (Argani et al. 2016).

Molecular Pathology

Distinguishing between the two types of PEComas is important because only Group B PEComas, particularly those found in the soft tissues, frequently harbor mutations involving *TSC2* and less frequently (approximately 25% of cases) *TSC1* (Thway and Fisher 2015; van Slegtenhorst et al. 1997). These mutations lead to activation of the mammalian target of rapamycin (mTOR) pathway (Goncharova et al. 2002; Martin et al. 2004), which can be therapeutically targeted by mTOR inhibitors (Wagner et al. 2010). Malignant Group B uterine PEComas harbor *TSC* mutations less frequently than PEComas occurring elsewhere; a recent study found that only 2 of 15 malignant uterine PEComas were found to harbor a *TSC2* mutation and none had a *TSC1* mutation (unpublished observations). Group A PEComas lack such mutations (Agaram et al. 2015) and therefore would not respond to mTOR blockade. Instead, chromosomal fusions involving TFE3 at the Xp11.2 locus are characteristic of these tumors, as discussed below.

Immunohistochemistry

Immunostaining is essential to confirm the diagnosis of PEComa, although two provisos must be kept in mind: (1) immunophenotype differs between group A and B PEComas, and (2) the immunophenotype of group B PEComas overlaps substantially with that of uterine smooth muscle tumors, particularly epithelioid smooth muscle tumors.

Group A PEComas show diffuse cytoplasmic staining with HMB-45 and cathepsin K along with strong and diffuse staining of tumor cell nuclei with TFE3 (Fig. 38). They are negative or only focally weakly positive for Melan-A, microphthalmia transcription factor (MITF), SMA, desmin, and caldesmon, and negative for SOX10 (Schoolmeester et al. 2015). Strong and diffuse TFE3 expression is the result of chromosomal translocations involving the *TFE3* transcription factor gene, which maps to the Xp11.2 locus. One of the *TFE3* fusion partners is *SFPQ/PSF* (Agaram et al. 2015), but the full repertoire of fusion partners is not yet known. Strong and diffuse nuclear TFE3 staining usually correlates well with the presence of a *TFE3* translocation identified with fluorescence in situ hybridization (FISH); any equivocal immunohistochemical result should be verified by FISH. When the differential diagnosis includes metastatic Xp11 translocation-associated renal cell carcinoma, PAX8 expression confirms that diagnosis, while a negative result would be more supportive of a group A PEComa (Argani et al. 2016). ASPS, which also features

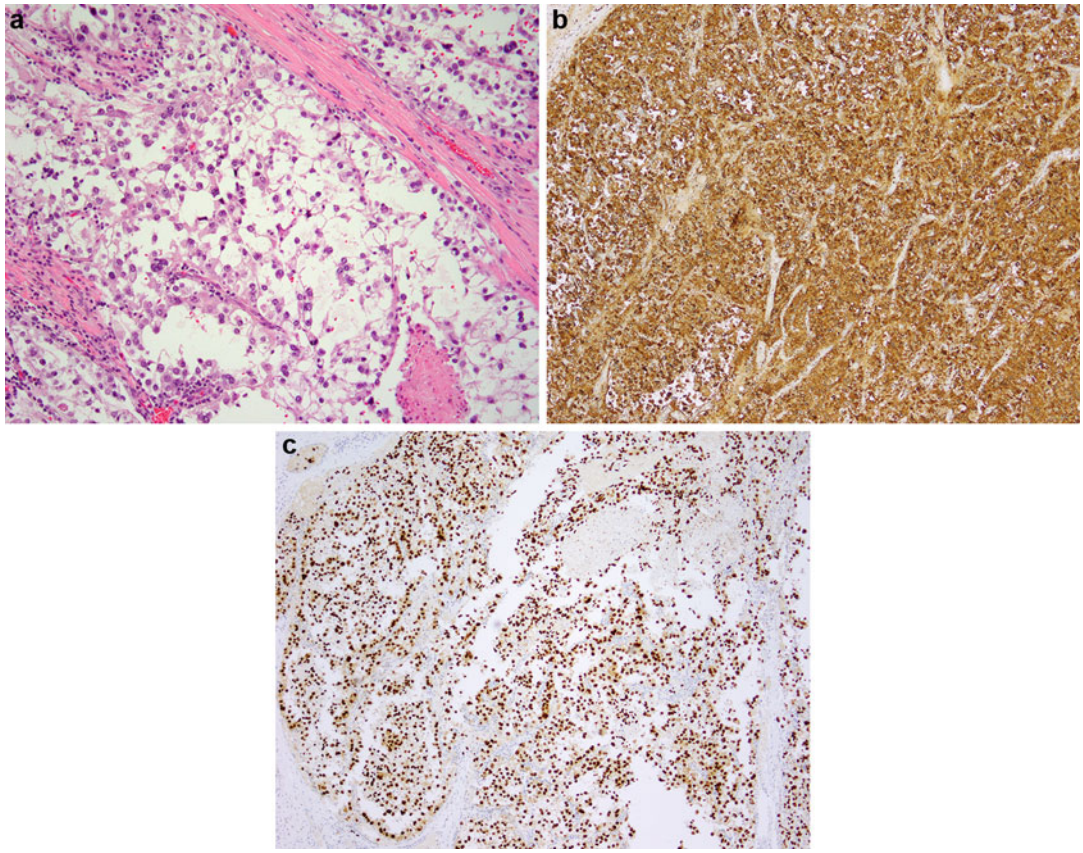

Fig. 38 PEComa (group A; TFE3-translocated/Xp11 PEComa). (**a**) Alveolar and solid aggregates of epithelioid tumor cells with clear cytoplasm are surrounded by a prominent vasculature, reminiscent of renal cell carcinoma of clear cell type and certain translocation-associated renal cell carcinomas. (**b**) Diffuse, strong staining for HMB-45 (compare to Fig. 37b). (**c**) Diffuse overexpression of TFE3 in tumor cell nuclei. The presence of a chromosomal translocation involving TFE3 can be confirmed by FISH

a TFE3 translocation involving Xp11.2, would not display diffuse HMB45, actin, or PAX8 staining.

In group B PEComas, the most characteristic finding is patchy positive HMB-45 staining of tumor cell cytoplasm (Fig. 37). Other melanocytic markers such as Melan-A and MiTF are also often positive; S-100 can be positive but is more often negative (Folpe et al. 2005). Positive staining for smooth muscle markers, most commonly smooth muscle actin and sometimes caldesmon or desmin, is also typical (Fukunaga 2005; Schoolmeester et al. 2014). Cytokeratin, CD117, and CD34 are generally negative. Electron microscopic study of one uterine PEComa that showed positive immunostaining for HMB-45 revealed pre-melanosomes in the tumor cells (Park et al. 2003). Despite the fact that these immunophenotypic characteristics are considered confirmatory of PEComa, many uterine smooth muscle tumors have nearly identical immunophenotypes (Fadare 2008; Oliva et al. 2006; Silva et al. 2004, 2005; Simpson and Albores-Saavedra 2007). Although it has been posited that co-expression of a muscle marker with two melanocyte-associated markers in a tumor that resembles PEComa is sufficient to make that diagnosis, this criterion has not been validated against a gold standard (Schoolmeester et al. 2014) such as *TSC1* or *2* mutation.

HMB-45 is not a specific marker of PEComa; positive HMB-45 staining has been reported in conventional and epithelioid uterine leiomyosarcomas (Hurrell and McCluggage 2005; Silva et al. 2004) and in metastases from an epithelioid leiomyosarcoma (Silva et al. 2005). In at least one case, a conventional uterine leiomyosarcoma has metastasized to the lung in the form of a purely epithelioid tumor with strong HMB45 expression. Retrospective review of the uterine primary disclosed a minute focus of malignant epithelioid cells that expressed HMB45, unlike the preponderant conventional components (unpublished observations, RAS). Because criteria for malignancy in PEComa are more permissive than for uterine smooth muscle tumors and metastatic PEComa is treated using mTOR inhibitors unlike leiomyosarcoma which is treated with chemotherapy, every effort should be made to distinguish these two tumor types.

The differential diagnosis includes endometrial stromal sarcoma (HMB-45 negative), metastatic melanoma (S100 positive), ASPS (smooth muscle marker and HMB45-negative) (Schoolmeester et al. 2017), and epithelioid smooth muscle neoplasms. As discussed previously, there is dispute about whether group B PEComas are a distinct type of neoplasm or a variant of a smooth muscle neoplasm. Along these lines, there has been some work to identify PEComa-specific biomarkers, such as beta catenin (Schoolmeester and Park 2015), cathepsin K (Rao et al. 2013), and CD1a (Ahrens and Folpe 2011), among others. Cathepsin K is also expressed in uterine smooth muscle tumors, limiting its diagnostic utility, and CD1a expression has been interpreted by some as an artifact. Until the controversy is resolved, it is best to classify a tumor with the morphologic and immunohistochemical features of leiomyosarcoma as such, regardless of whether it stains for HMB-45. Uterine tumors that very closely resemble PEComas that occur in extrauterine sites may be considered candidates for that diagnosis, but such diagnoses should be verified by testing for *TSC1* or *2* mutations or activation of the mTOR pathway, particularly if the tumor is obviously malignant. Group B PEComas may exist as two types: those that arise de novo or in association with "PEComatosis" and those that arise in the background of a uterine smooth muscle tumor.

HMB-45 staining is also typical of other tumors in the PEComa family; those that are occasionally detected in the uterus include LAM and angiomyolipoma. In angiomyolipoma, a benign tumor, HMB-45 positive tumor cells are present in the fat and among the smooth muscle cells. In LAM, which is generally a microscopic finding (Gyure et al. 1995; Torres et al. 1995), some smooth muscle cells (Fig. 39) show positive staining for HMB-45.

Clinical Behavior and Treatment

Both benign and malignant variants of PEComa (based on the extent of tumor at diagnosis or clinical follow-up) have been reported (Dimmler et al. 2003; Greene et al. 2003). In one recent review, 44% of corpus cases were classified as malignant and 56% as benign (Fadare 2008). Features proposed as being predictive of an unfavorable outcome include large size (>5 cm), high cellularity, significant nuclear atypia, mitotic activity (>1 MF/10 HPF), coagulative tumor cell necrosis, invasive growth, and lymphovascular space invasion (Folpe et al. 2005). Other slight

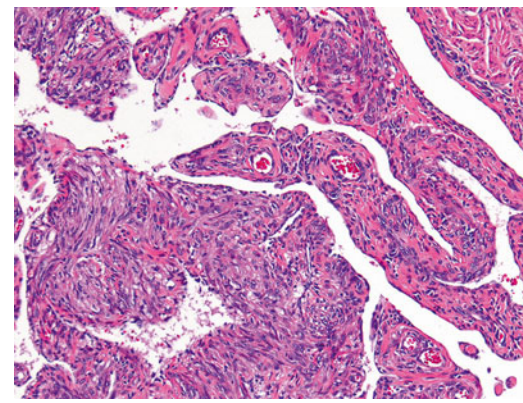

Fig. 39 LAM involving the myometrium. The tumor cells are usually spindled with oval nuclei and flocculent eosinophilic cytoplasm. The growth is centered on dilated lymphovascular spaces, and intravascular growth is typically present, often at the periphery of the area of involvement. Sometimes, it mimics the appearance of intravascular endometrial stromal sarcoma

variations on this theme have been published (Conlon et al. 2015). As mentioned, mTOR inhibitors may be used for group B metastatic malignant PEComas, while treatment for group A PEComas has not been studied.

Endometrial Stromal Tumors

Endometrial stromal tumors represent the second most common category of mesenchymal tumors of the uterus, but they are by far much less common than smooth muscle tumors and overall account for less than 10% of all uterine mesenchymal tumors and up to 25% of all uterine sarcomas (Abeler et al. 2009). In the latest WHO classification, they are divided into four categories: (a) endometrial stromal nodule, (b) low-grade endometrial stromal sarcoma, (c) high-grade endometrial stromal sarcoma, and (d) undifferentiated uterine sarcoma (Table 8). The high-grade category was reintroduced based on its distinct morphologic, immunohistochemical, and molecular characteristics (Oliva et al. 2014). Terminology for the last category was changed from "undifferentiated endometrial stromal sarcoma" to "undifferentiated uterine sarcoma" as some of these tumors may have a smooth muscle or other cell of origin. Among these categories, low-grade endometrial stromal sarcoma is by far the most common, but still only represents <0.5% of all malignant tumors of the uterus. For practical purposes, endometrial stromal nodule and low-grade endometrial stromal sarcoma will be discussed together in this chapter. The main difference between the two categories is myometrial or vascular invasion, which distinguishes benign (endometrial stromal nodule) from malignant (low-grade endometrial stromal sarcoma); otherwise, they share histologic, immunohistochemical, and molecular features.

Endometrial Stromal Nodule and Low-Grade Endometrial Stromal Sarcoma

Clinical Features

Endometrial stromal nodules are rare, while endometrial stromal sarcomas have an annual incidence of ~1–2 per 1 million women (Hendrickson et al. 2003). Endometrial stromal nodules tend to occur in perimenopausal women, but they have been reported within a wide age range (20–86 years). Endometrial stromal sarcomas tend to be seen in women between 40 and 55 (range, 16–83) years, a younger age at diagnosis compared to other uterine sarcomas (mean 60 years) (Xue and Cheung 2011). Patients often present with abnormal uterine bleeding, but they may complain of pelvic/abdominal pain or have an enlarged uterus or pelvic mass on gynecologic exam, or the tumor may be an incidental finding during surgery for other reasons, usually leiomyomas (Chang et al. 1990; De Fusco et al. 1989; Dionigi et al. 2002; Fekete and Vellios 1984; Hart and Yoonessi 1977; Norris and Taylor 1966; Tavassoli and Norris 1981). Low-grade endometrial stromal sarcoma has been associated with prolonged use of estrogen or tamoxifen as well as pelvic radiation (Beer et al. 1995; Eddy and Mazur 1997; Meredith et al. 1986; Press and Scully 1985). Occasionally, patients with endometrial stromal sarcoma may present initially at a metastatic site, most commonly the lungs or ovary (Aubry et al. 2002; Young et al. 1984; Young and Scully 1990).

Table 8 Classification of endometrial stromal tumors

Tumor	Category	Cytologic atypia
Stromal nodule	Benign	Minimal
Low-grade endometrial stromal sarcoma	Malignant, low grade	Minimal
High-grade endometrial stromal sarcoma		
YWHAE-FAM22	Malignant, intermediate	Uniform
ZC3H7B-BCOR	Malignant, intermediate	Moderate
Arising from low-grade endometrial stromal sarcoma	Malignant, high grade	Marked
Undifferentiated uterine sarcoma	Malignant, high grade	Marked

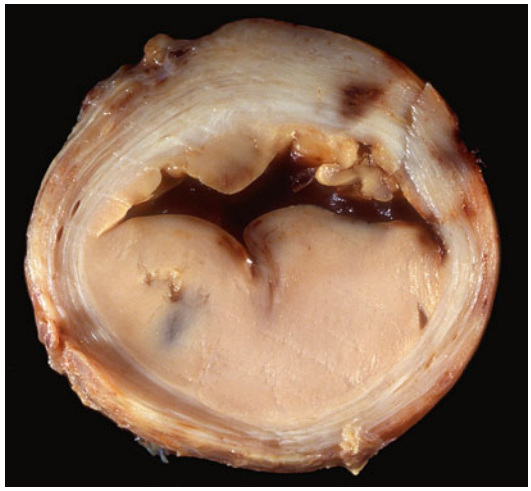

Fig. 40 Endometrial stromal nodule. The tumor is well circumscribed from the surrounding myometrium and has a homogeneous tan cut surface with central cystic change

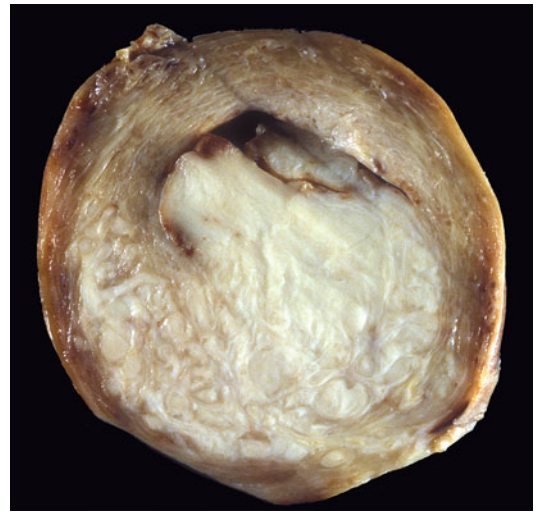

Fig. 41 Low-grade endometrial stromal sarcoma. Tan-to-white polypoid tumor centered in the endometrium protrudes into the uterine cavity and irregularly infiltrates the myometrium as "worm-like" plaques resulting in a thickened myometrial wall

Gross Findings

Endometrial stromal nodules are typically well circumscribed with pushing borders, centered in the myometrium or endometrium, with sizes ranging from <1 to 25 cm. They typically display a solid, tan-to-yellow, homogenous cut surface, often with one or several cysts filled with hemorrhagic fluid; rarely they may be predominantly cystic (Fig. 40). Areas of necrosis and hemorrhage may be noted (Chang et al. 1990; Dionigi et al. 2002; Tavassoli and Norris 1981). In contrast, endometrial stromal sarcomas are poorly circumscribed and characterized by coalescent soft, yellow-to-tan-to-whitish rounded nodules that invade the myometrium, as well as worm-like plugs of tumor-filling myometrial and sometimes parametrial veins (the latter easier to appreciate) (Figs. 41 and 42). They often contain a polypoid endometrial component. However, some endometrial stromal sarcomas may be deceptively well circumscribed on gross examination, so extensive sampling of the tumor myometrial interface is necessary to distinguish between the two entities (Dionigi et al. 2002). Areas of hemorrhage and necrosis may be seen (Chang et al. 1990; Fekete and Vellios 1984; Hart and Yoonessi 1977; Norris and Taylor 1966); they are only rarely predominantly cystic.

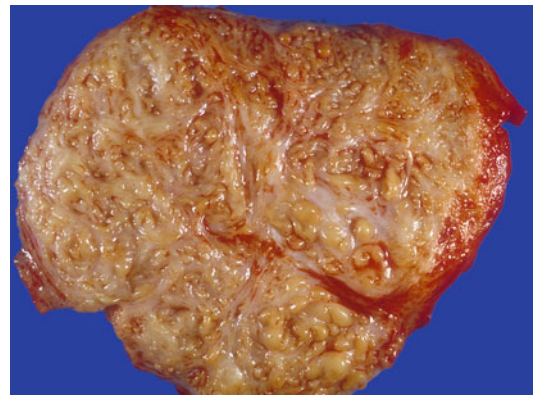

Fig. 42 Low-grade endometrial stromal sarcoma. Tumor infiltrating the myometrium, causing a trabeculated cut surface

Both endometrial stromal nodules and low-grade endometrial stromal sarcoma may display variant morphology. Those with smooth muscle differentiation may contain firmer and whiter areas (corresponding to smooth muscle differentiation) in a soft tan-to-yellow background (typical of endometrial stromal neoplasia) (Oliva

et al. 1998). Tumors with myxoid background may have a gelatinous, sticky cut surface, while those with fibroblastic background may display a firm and white cut surface that closely resembles that of a typical leiomyoma (Oliva et al. 1999).

Microscopic Findings

On microscopic examination, endometrial stromal nodule is defined by the WHO classification as a tumor with well-circumscribed margins (Fig. 43) with or without limited irregularities (<3), seen as finger-like projections or nests of tumor cells immediately adjacent to the main mass measuring <3 mm in greatest extent (Fig. 44). The presence of lymphovascular invasion excludes the diagnosis of endometrial stromal nodule (Oliva et al. 2014). In contrast, low-grade endometrial stromal sarcoma is characterized by a "tongue-like" permeative pattern of invasion into the myometrium by irregularly sized and shaped nests of tumor cells without an associated stromal response (Figs. 45 and 46) and, frequently, lymphovascular invasion (Fig. 47) (Oliva et al. 2014).

Although they differ in terms of myometrial and vascular invasion, endometrial stromal nodule and low-grade endometrial stromal sarcoma have identical high-power appearances, reminiscent of proliferative phase endometrium. They typically display a diffuse growth of small uniform cells with scant cytoplasm, oval to slightly fusiform nuclei, inconspicuous nucleoli, and bland cytologic features (Fig. 48a). Occasionally, they may have more abundant amphophilic cytoplasm due to decidualization. Mitotic activity is low (usually <5 MF/10 HPF), but higher rates may be seen in both endometrial stromal nodules (up to 24 MF/10 HPF) and low-grade endometrial stromal sarcomas (up to 32 MF/10 HPF). Although tumors are typically hypercellular ("blue"), they may be variably cellular, some displaying extensive areas of edema or hyalinization. Typical arteriole-like vessels are common and may be hyalinized but are infrequently conspicuous within a neoplasm (Fig. 48b); tumor cells may whorl around them. Curvilinear thin and/or small ectatic vessels are also common, but thick, large vessels are rare,

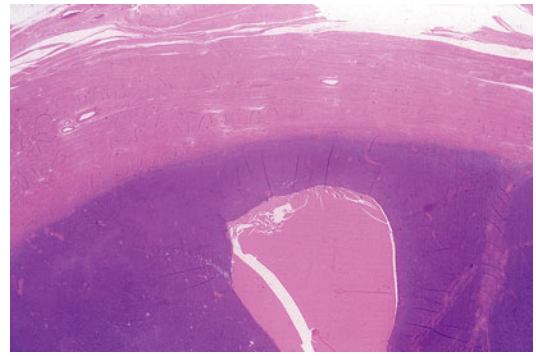

Fig. 43 Endometrial stromal nodule. The well-defined interface with the myometrium is a defining feature of this tumor

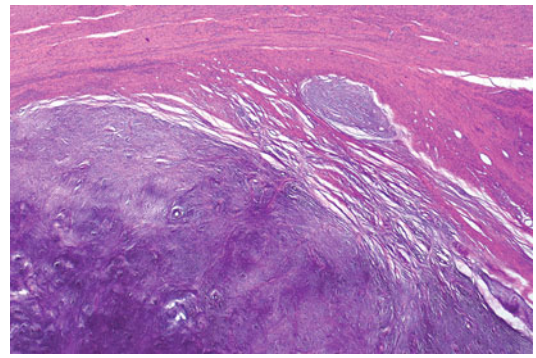

Fig. 44 Endometrial stromal nodule. Although the tumor is mostly well circumscribed, the margin is focally irregular, with a small satellite nest <3 mm from the main nodule. There is no lymphovascular invasion

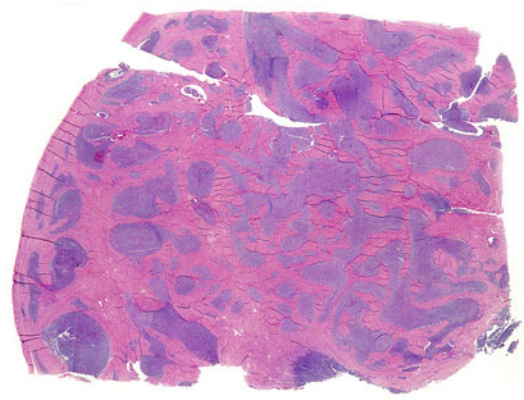

Fig. 45 Low-grade endometrial stromal sarcoma. On low-power microscopic examination, irregular islands of "blue cells" permeate the myometrium

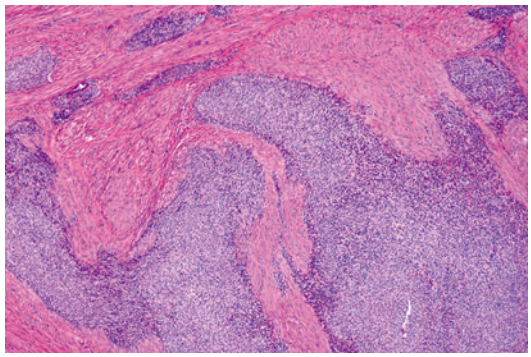

Fig. 46 Low-grade endometrial stromal sarcoma. Irregular tongues and prongs of tumor cells invade the myometrium and are unassociated with stromal response

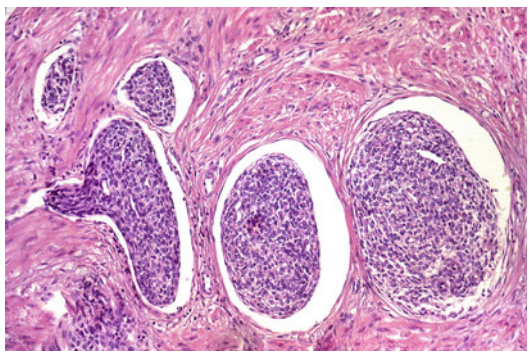

Fig. 47 Low-grade endometrial stromal sarcoma. Vascular invasion, a common finding in these tumors, can be seen within the myometrium or parametrial veins, which can be highlighted by staining for CD31 but not D2-40 (the latter is a marker of lymphatic spaces)

typically entrapped at the periphery. Hyaline bands or plaques may be seen and be prominent (Fig. 49).

Endometrial stromal nodules and low-grade sarcomas may also contain cysts, inflammatory cells, and necrosis. Cysts are more common in endometrial stromal nodules, in which they are centrally located and lined by stromal cells, foamy histiocytes, or both; the latter may be also seen in groups or in isolation admixed with tumor cells and/or cholesterol clefts and rarely may form large aggregates. Tumors may contain inflammatory cells, usually lymphocytes. Necrosis, only rarely encountered, is typically of infarct type, which may be associated with recent or old hemorrhage (Abeler et al. 2009; Chang et al. 1990). Rarely areas of calcification or even ossification can be noted. As all morphologic features mentioned above can be encountered in both stromal nodule and low-grade endometrial stromal sarcoma, a specific diagnosis cannot typically be rendered on a curettage specimen, as the margins of the tumor cannot be assessed (Nucci 2016; Oliva et al. 2000).

Variant morphologic features seen in these two categories of tumors (Table 9) include smooth muscle, skeletal muscle, sex cord-like, glandular, and adipocytic (Baker et al. 2005) differentiation as well as fibrous and/or myxoid, pseudopapillary or papillary, rhabdoid, epithelioid and/or granular (Dionigi et al. 2002; Oliva et al. 2002a), clear appearance (Lifschitz-Mercer et al. 1987), and

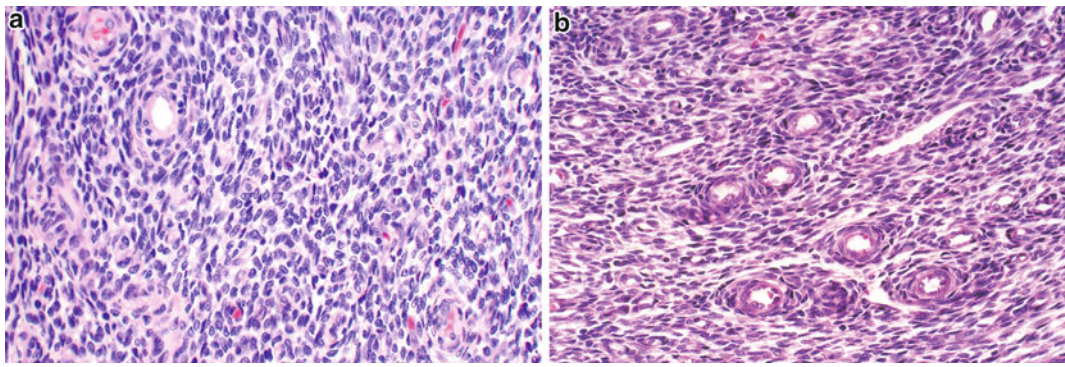

Fig. 48 Endometrial stromal nodule and low-grade endometrial stromal sarcoma are both cellular and composed of uniform bland cells with scant cytoplasm and oval nuclei, (**a**) Small vessels reminiscent of arterioles are often noted, and the tumors have an overall appearance reminiscent of proliferative-type endometrium (**b**)

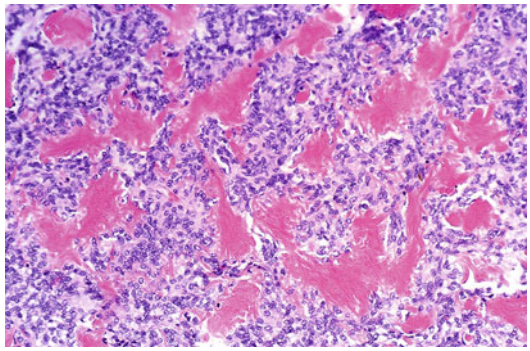

Fig. 49 Low-grade endometrial stromal sarcoma. Eosinophilic hyaline bands and plaques may be variably present in endometrial stromal nodules and low-grade endometrial stromal sarcomas. Although characteristic of this group of tumors, they are rarely seen in smooth muscle tumors

Table 9 Variant morphologies in endometrial stromal tumors (nodules and low-grade endometrial stromal sarcomas)

Smooth muscle
Skeletal muscle
Sex cord-like
Fibroblastic and/or myxoid
Endometrioid glandular
Pseudopapillary or papillary[a]
Adipocytic[a]
Rhabdoid
Epithelioid and/or granular (polygonal cells with easily appreciated cytoplasm)[a] or clear cytoplasm
Cells with bizarre nuclei[a]
Osteoclast-like[a]

[a]Only very rare examples are on record

cells with bizarre nuclei (Baker et al. 2005; Kibar et al. 2008; Shah and McCluggage 2009) or osteoclast-like cells (Fadare et al. 2005). More than one feature may be seen within one tumor, and not infrequently smooth muscle and sex cord-like differentiation coexist. As these morphologic variants may be seen in the primary or metastatic setting, the metastatic tumor may have an appearance completely different from the primary uterine tumor (Yilmaz et al. 2002).

Smooth muscle differentiation is morphologically characterized at low power magnification by small nests of rounded to slightly irregular nodules with prominent central hyalinization, from which collagen bands radiate toward the periphery. The collagen bands embed rounded cells ("starburst pattern") that transition to disorganized short fascicles that in turn form longer fascicles of spindle cells with eosinophilic cytoplasm, cigar-shaped nuclei, bland cytologic features, and low mitotic activity (Fig. 50). This smooth muscle component is often seen at the periphery of the tumor, may be predominant, may rarely display malignant cytologic features, or may be the sole component at a metastatic site (Dionigi et al. 2002; Kim et al. 1996; McCluggage et al. 2001a; Oliva et al. 1998; Schammel et al. 1999; Yilmaz et al. 2002). Smooth muscle differentiation has been reported by morphologic, immunohistochemical, and electron microscopic studies (Binder et al. 1991; Chang et al. 1990; Devaney and Tavassoli 1991; Dionigi et al. 2002; Fekete and Vellios 1984; Hart and Yoonessi 1977; Kim et al. 1996; Lloreta and Prat 1992; McCluggage et al. 2001a; Oliva et al. 1998; Tavassoli and Norris 1981; Yilmaz et al. 2002), but a diagnosis of smooth muscle differentiation requires that it represent >30% of the tumor by hematoxylin-eosin evaluation (Oliva et al. 2014). The term "stromomyoma" is discouraged, as it has benign implications. For diagnostic and prognostic purposes, the tumor should be reported based on its margins as an endometrial stromal nodule or low-grade endometrial stromal sarcoma with smooth muscle metaplasia. Skeletal muscle differentiation (Baker et al. 2005; Lloreta and Prat 1992, 1993) is far less frequent than smooth muscle differentiation but can very rarely be seen in combination. Cells may be large and round, with abundant bright eosinophilic cytoplasm and abundant filaments in a perinuclear distribution, or may have a strap-shaped morphology and easily identified cross striations (Baker et al. 2005; Lloreta and Prat 1992, 1993).

Sex cord-like differentiation can be seen in endometrial stromal nodules and low-grade endometrial stromal sarcomas and can be quite prominent. It may display anastomosing cords, trabeculae, nests, islands, tubules, and diffuse growth in variable combinations (Fig. 51). Cords, trabeculae, nests, islands, and diffuse growth recapitulate the appearance of adult

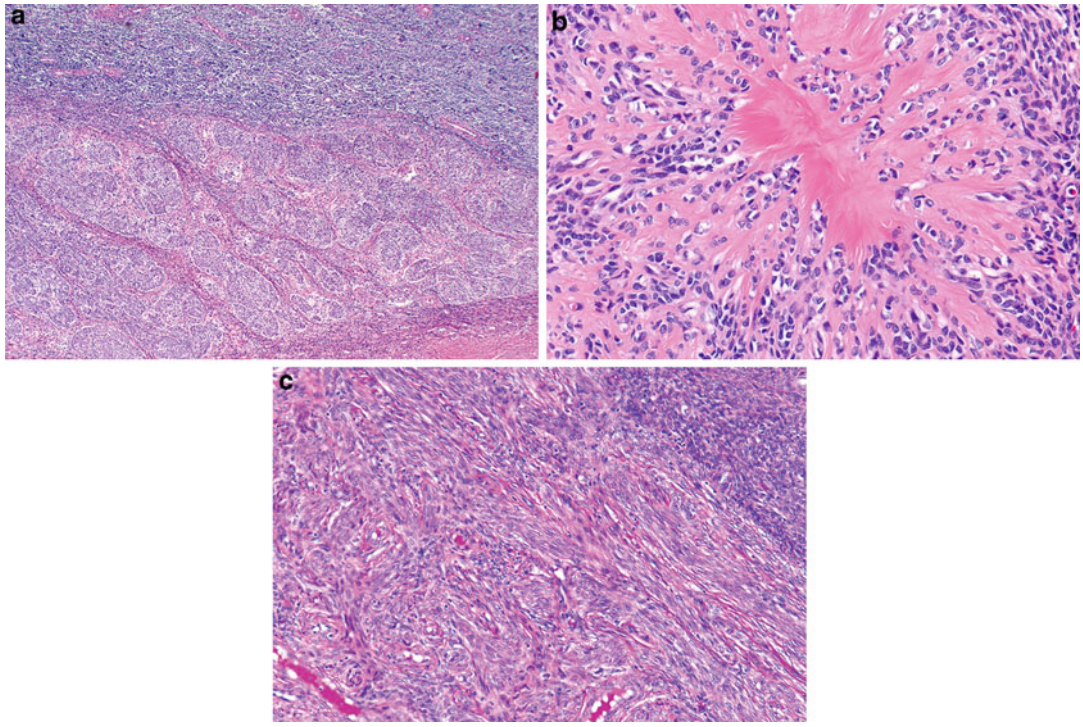

Fig. 50 Endometrial stromal tumor with smooth muscle differentiation. (**a**) Small nests/nodules of smooth muscle cells are juxtaposed against sheets of small dark blue cells. (**b**) Starburst appearance, with a central area of hyalinization and collagen bands radiating toward its periphery embedding rounded cells, is the most characteristic pattern of smooth muscle differentiation. (**c**) Small fascicles of spindle cells are often seen at the periphery of the hyalinized rounded nodules and/or adjacent to areas of endometrial stromal neoplasia

granulosa cell tumors of the ovary (Fig. 51). The cells often display relatively scant eosinophilic cytoplasm and slightly irregular nuclei typically without grooves. Tubules may be hollow or solid, lined by cells with eosinophilic or vacuolated cytoplasm and round to oval nuclei, or have a retiform appearance with small papillae as noted in Sertoli cell/Sertoli-Leydig cell tumors of the ovary. Not infrequently sex cord-like differentiation coexists with smooth muscle differentiation. Rhabdoid morphology, characterized by prominent paranuclear arrays of intermediate filaments, may also be seen, especially in areas reminiscent of granulosa cell tumor (Clement and Scully 1976; D'Angelo et al. 2013; Fitko et al. 1990; Lillemoe et al. 1991; McCluggage et al. 1996; Rosty et al. 1998; Zamecnik and Michal 1998), though it can also be noted within the areas of conventional endometrial stromal neoplasia (Tanimoto et al. 1996).

Fibroblastic and/or myxoid background imparts a hypocellular appearance to the tumor at low-power magnification in contrast to the hypercellular nature of most endometrial stromal neoplasms (Kasashima et al. 2003; Kim et al. 2015; Oliva et al. 1999; Park et al. 2013; Yilmaz et al. 2002). Prominent delicate or dense collagen or myxoid (+/− microcysts) background is characteristic of these tumors (Fig. 52). In the fibroblastic variant, cells are arranged in a nodular, fascicular, or diffuse fashion; in myxoid tumors, there is a diffuse distribution of the tumor cells which are typically small with oval nuclei, and cytologically low grade. Areas of extensive hyalinization may occur. The vasculature and tongue-like pattern of invasion are similar to those seen in typical endometrial stromal sarcoma. At metastatic sites, the morphology may be similar to that seen in the uterus, but it also may be more cellular and reminiscent of a fibrosarcoma. This variant of

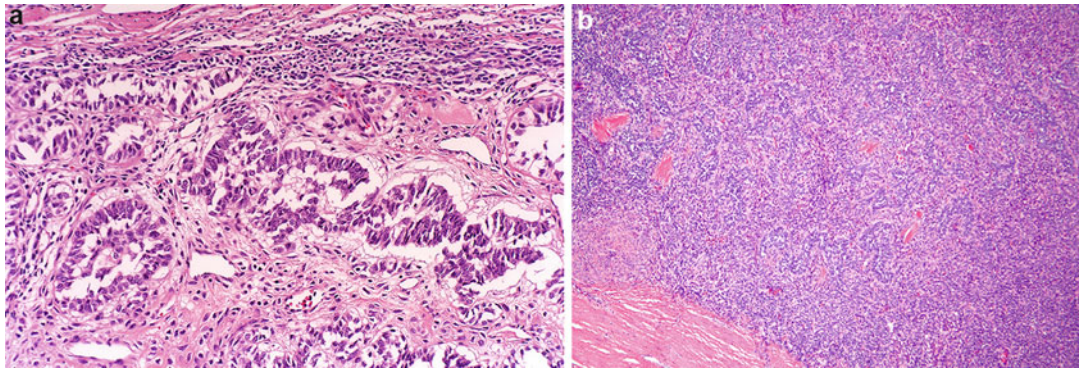

Fig. 51 Endometrial stromal tumor with sex cord-like differentiation. Cord-like structures (**a**), trabeculae, or tubules, some with retiform appearance (**b**), may be seen in variable extent in these tumors. When extensive, the differential diagnosis includes a UTROSCT

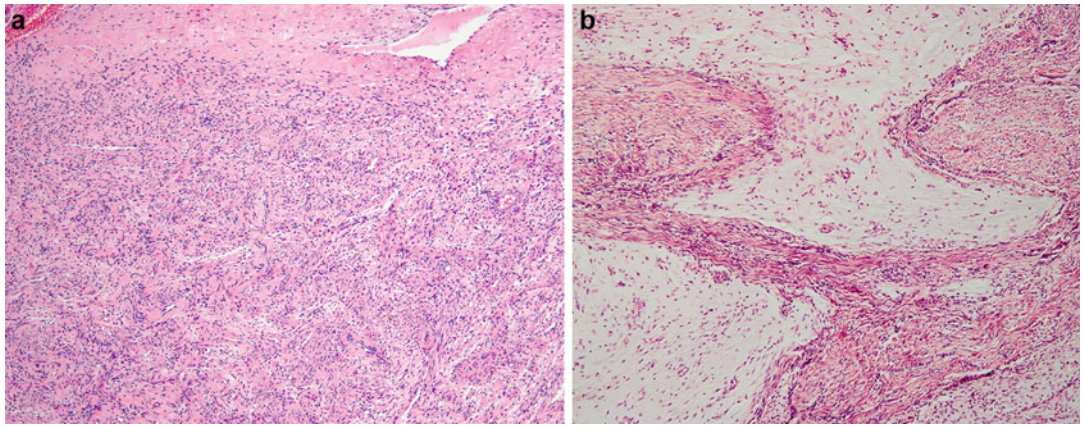

Fig. 52 Endometrial stromal tumor with fibroblastic and myxoid appearance. Some endometrial stromal tumors are hypocellular due to delicate fibroblastic/collagenous (**a**) or myxoid (**b**) background. Arterioles are typically seen in both categories of tumors; tongue-like infiltration is characteristic of endometrial stromal sarcoma

endometrial stromal sarcoma may be associated with YWHAE-FAM22 high-grade endometrial stromal sarcoma, discussed subsequently in this chapter (Lee et al. 2012b).

Endometrioid glandular differentiation may range from benign to atypical to carcinoma and can vary extensively in amount (Fig. 53) (Clement and Scully 1992; McCluggage et al. 2001a, 2009; Tavassoli and Norris 1981). Papillae and pseudopapillae are rarely seen in endometrial stromal tumors but can be the predominant morphology. This appearance can be seen invading the myometrium or within vascular spaces. Small, uniform cells with bland cytologic features, associated with the classic vasculature, constitute the papillae and pseudopapillae. (McCluggage and Young 2008).

Immunohistochemical and Molecular Pathology

Endometrial stromal nodule and low-grade endometrial sarcoma share the same immunohistochemical profile. Tumor cells are typically positive for CD10 (Fig. 54) with some exceptions. CD10, also known as common acute lymphoblastic leukemia antigen, has good sensitivity

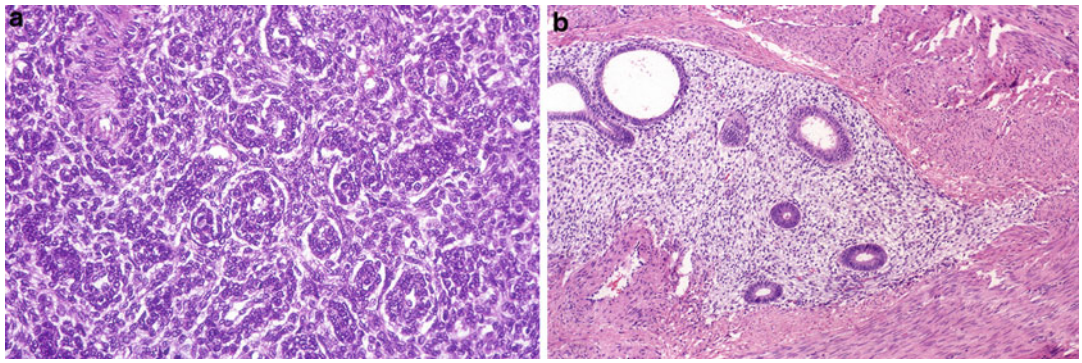

Fig. 53 Endometrial stromal tumour with glandular differentiation. Poorly developed epithelial-like differentiation (**a**) or well-developed endometrioid-type glands (**b**) are distributed focally in these tumors. Glands are typically lined by benign-appearing cells, although rarely may be atypical or malignant

(75–100%) for the diagnosis of a low-grade endometrial stromal tumor (Abeler and Nenodovic 2011; Chu and Arber 2000; Chu et al. 2001; McCluggage et al. 2001b; Oliva et al. 2002b; Toki et al. 2002). Expression of this marker is not always diffuse and strong in these tumors, and other neoplasms in the differential diagnosis, including highly cellular leiomyoma and leiomyosarcoma, may be positive, making this marker's specificity low (Abeler and Nenodovic 2011; D'Angelo and Prat 2010; Mikami et al. 2002; Oliva et al. 2002b). Interferon-inducible transmembrane protein-1 (IFITM1 or CD225) has emerged as a potential new marker of benign and malignant endometrial stroma (Fig. 55) (Parra-Herran et al. 2014). IFITM1 appears to have similar sensitivity but higher specificity than CD10 in distinguishing these tumors from smooth muscle tumors, but more studies are required to confirm these findings (Busca et al. 2017).

Other positive markers in endometrial stromal nodule and low-grade endometrial sarcoma include hormone receptors, keratins, smooth muscle markers, and β-catenin. ER (typically isoform α) is expressed in 40–100% and PR (Fig. 56) in 60–100% (isoform A being predominant) of low-grade endometrial stromal sarcomas, but expression is often heterogeneous (Balleine et al. 2004; Chu et al. 2003; Jakate et al. 2013; Navarro et al. 1992; Reich et al. 2000; Wu et al. 2013; Yoon et al. 2014); AR is expressed in a smaller

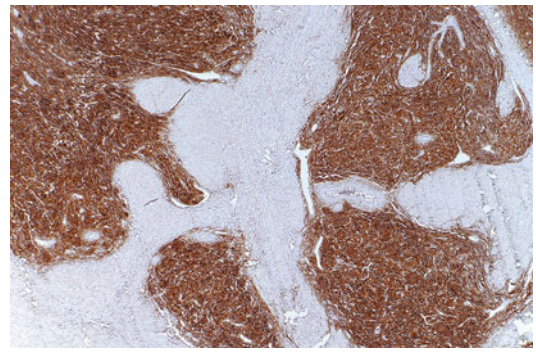

Fig. 54 Low-grade endometrial stromal sarcoma. Irregular nests of neoplastic stromal cells strongly express CD10, but staining intensity varies from tumor to tumor and on occasion CD10 is negative

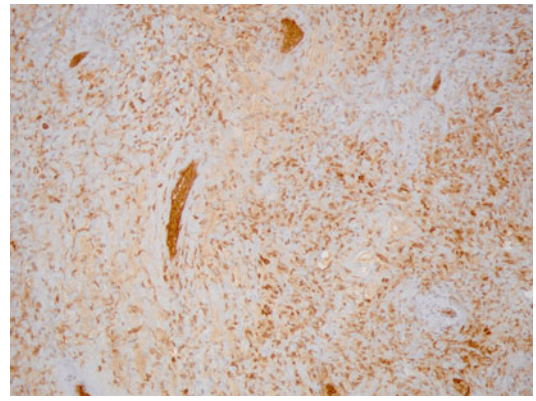

Fig. 55 IFITM1 cytoplasmic staining characteristic of endometrial stromal nodule and low-grade endometrial stromal sarcoma. IFITM1 may be a more specific marker compared with CD10

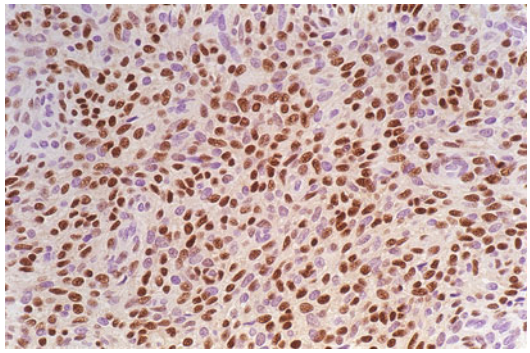

Fig. 56 Strong nuclear staining for progesterone, characteristic of most endometrial stromal nodules and low-grade endometrial stromal sarcomas. These tumors also express ER and less commonly AR. Hormonal status may indicate degree of aggressiveness of endometrial stromal sarcoma (some types of high-grade endometrial stromal sarcoma are negative for ER and PR)

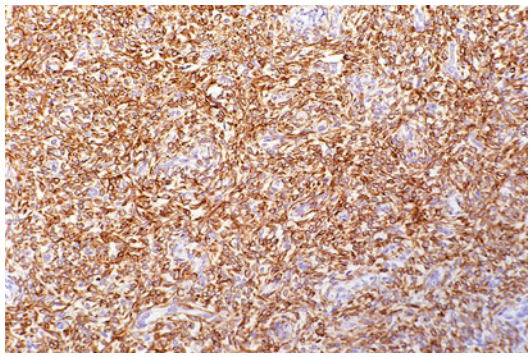

Fig. 57 Cytokeratin immunoreactivity in conventional low-grade endometrial stromal sarcoma. Cocktail (AE1/3-Cam5.2) may reveal strong expression

proportion of tumors (~50%) (Moinfar et al. 2004; Roy et al. 2017). Keratins expressed by these tumors include AE1/3, CAM 5.2 (Fig. 57), MNF116, and CK8/18 (Agoff et al. 2001; Binder et al. 1991; Farhood and Abrams 1991; Rahimi et al. 2018; Sumathi et al. 2004). Smooth muscle markers may be positive in conventional areas of endometrial stromal neoplasia, more frequently smooth muscle actin and calponin (Oliva et al. 2002b), uncommonly desmin (Fig. 58), and rarely caldesmon, HDCA8, and smooth muscle myosin (Abrams et al. 1989; Franquemont et al. 1991). Smooth muscle actin, desmin, caldesmon (Fig. 59), and HDCA8 are often positive in areas of smooth muscle differentiation (de Leval et al. 2006; Irving et al. 2006; Lillemoe et al. 1991; Nucci et al. 2001; Oliva et al. 2002b; Rush et al. 2001), but desmin may also be positive in tumors with fibroblastic morphology (Oliva et al. 1999). Nuclear β-catenin staining has been reported but without associated mutations (Jung et al. 2008; Ng et al. 2005). Less than half of low-grade endometrial stromal sarcomas display aromatase expression (Reich and Regauer 2004). Areas of sex cord differentiation may be positive for inhibin (Fig. 60a), calretinin, CD99 (Fig. 60b), melanA, WT1, and less commonly CD56, and also frequently express keratins and smooth muscle markers (Baker et al. 1999; Fukunaga et al. 1997; Irving et al. 2006; McCluggage et al. 1996; McCluggage and Young 2008; Ohta et al. 2010; Zamecnik and Michal 1998), but they are negative

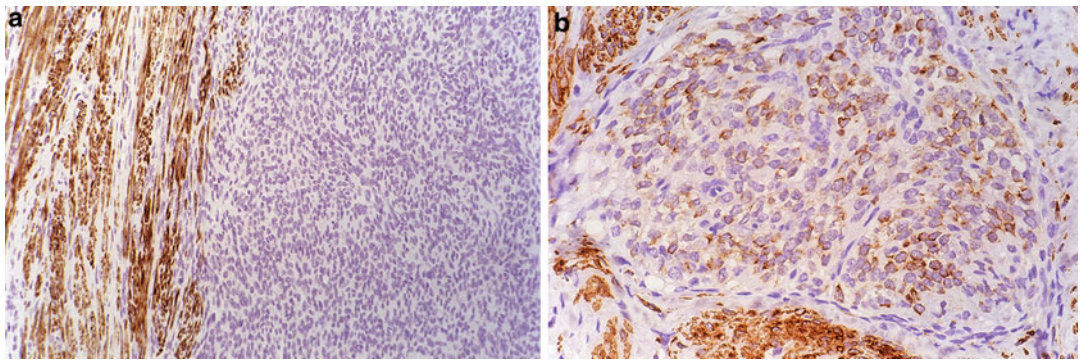

Fig. 58 Staining for desmin in conventional low-grade endometrial stromal sarcoma. (**a**) This marker is often not expressed. (**b**) Some tumors may show weak staining, including tumors with fibroblastic appearance. Smooth muscle actin is often expressed in these areas, but typically not caldesmon

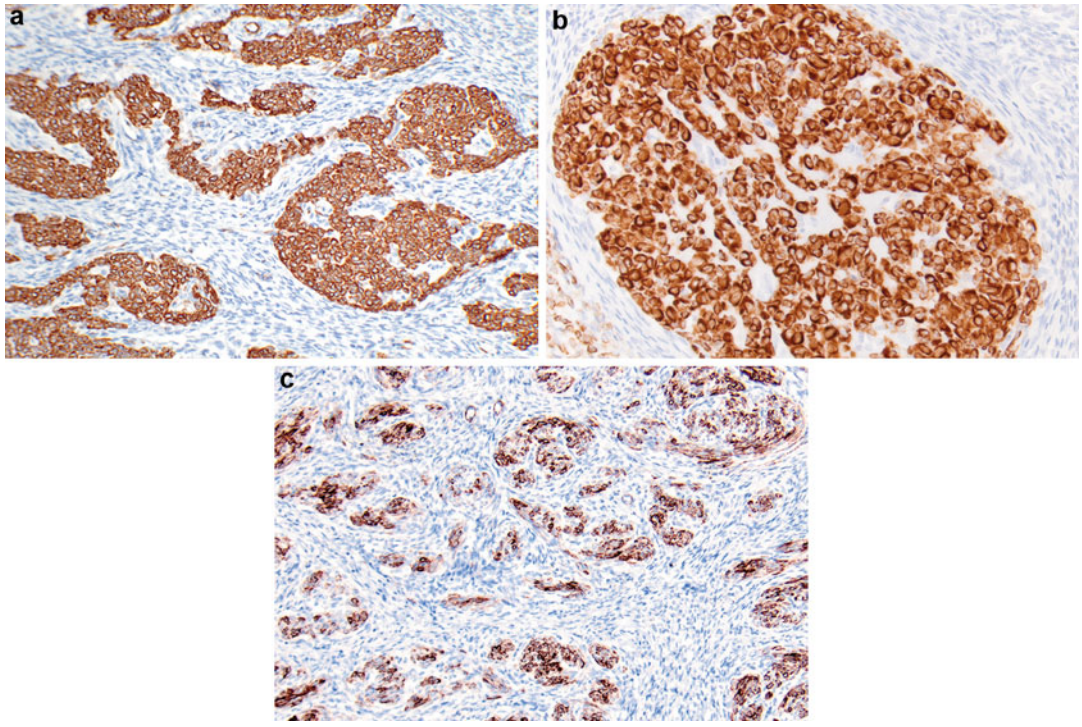

Fig. 59 Expression of smooth muscle markers in areas of smooth muscle differentiation within endometrial stromal tumors. (**a**) nests (smooth muscle actin); (**b**) starburst areas (desmin); (**c**) small fascicles (caldesmon)

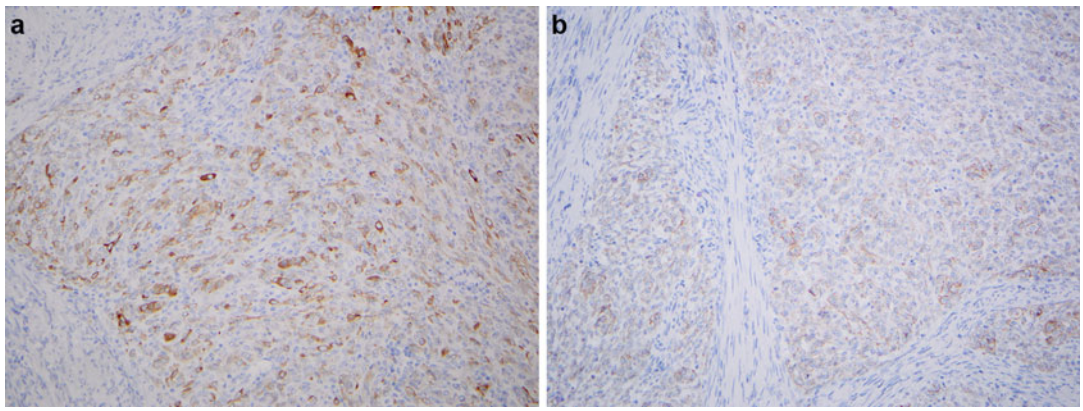

Fig. 60 Inhibin (a) and CD99 (b) are variably expressed in areas of sex cord-like differentiation within endometrial stromal tumors

for FOXL2 (Stewart et al. 2008). Staining for BCOR, DOG1, cyclin D1, and c-kit is typically negative; staining for the latter two markers may be focally positive, but no associated mutations have been detected (Kurihara et al. 2008; Rushing et al. 2003).

Endometrial stromal nodules and low-grade endometrial stromal sarcomas, especially with conventional morphology, harbor *JAZF1-SUZ12* fusions (~70% and 50%, respectively) most frequently followed by *JAZF1-PHF1* (~6%), *EPC1-PHF1* (4%), *MEAF6-PHF1* (3%),

ZC3H7B-BCOR (2%), *MBTD1-CXorf67* (2%), and BRD8-PHF1 fusions (Chiang et al. 2011; Croce et al. 2013; Dal Cin et al. 1992; Dewaele et al. 2014; Hennig et al. 1997; Hrzenjak 2016; Koontz et al. 2001; Lee et al. 2012c; Micci et al. 2003, 2006, 2014, 2017; Nucci et al. 2007; Panagopoulos et al. 2012, 2013; Pauwels et al. 1996; Satoh et al. 2003). The shared finding of JAZF1-SUZ12 gene fusion in at least 70% of endometrial stromal nodules and a significant proportion of low-grade endometrial stromal sarcomas suggests that *JAZF1-SUZ12* fusion may be an early event in the development of these tumors and could be used as a diagnostic tool. On the other hand, the rare finding of identical translocations in undifferentiated sarcomas seen next to endometrial stromal sarcomas indicate that some 'undifferentiated sarcomas' represent transformation from low- to high-grade endometrial stromal sarcoma. Endometrial stromal tumors with smooth muscle, sex cord, or fibroblastic morphology have been shown to harbor similar gene fusions, albeit less commonly (Ali et al. 2014; Chiang et al. 2011; D'Angelo et al. 2013; Huang et al. 2004; Oliva et al. 2007; Stewart et al. 2014). These translocations can be detected by a variety of methods including cytogenetics, FISH, or RT-PCR.

Differential Diagnosis

Due to their wide morphologic spectrum, the differential diagnosis of endometrial stromal tumors is extensive, including benign and malignant entities, but first, two important aspects should be highlighted in the distinction of endometrial stromal nodule from low-grade endometrial stromal sarcoma. The first is the existence of endometrial stromal tumors with limited infiltration. These tumors are suspected to be endometrial stromal nodules on gross examination, but extensive sampling of the tumor-myometrial interface reveals more extensive infiltration of the myometrium (irregularities up to 9 mm and up to 6 in number) compared with stromal nodules, which may show limited irregularities (fewer than three foci measuring <3 mm) at the interface between tumor and myometrium. While these tumors likely will have a better prognosis compared to typical endometrial stromal sarcomas, they should be diagnosed as low-grade endometrial stromal sarcoma with an explanatory note (Dionigi et al. 2002). The other issue is mistaking smooth muscle differentiation in an endometrial stromal tumor as myometrium, which results in misdiagnosis of endometrial stromal nodule as endometrial stromal sarcoma. In these cases, the gross appearance of the margin should be evaluated (Oliva et al. 1998).

Highly cellular leiomyoma is the most common entity in the differential diagnosis of both endometrial stromal nodule and low-grade endometrial stromal sarcoma (conventional or with smooth muscle differentiation), as all share dense cellularity and prominent vasculature. Furthermore, highly cellular leiomyomas often have a tan-to-yellow cut surface and may show an irregular margin with the adjacent myometrium and be positive for CD10 (some extensively), which are typical features of endometrial stromal tumors. However, highly cellular leiomyomas typically have a fascicular growth of spindle cells that contrasts with the diffuse growth of ovoid cells seen in endometrial stromal tumors. They also display large and thick blood vessels, as well as cleft-like spaces. Though their interface with the myometrium may be irregular, the neoplastic cells merge with the surrounding myometrium. Furthermore, these tumors are typically positive for desmin, caldesmon, and HDAC8 (de Leval et al. 2006; Oliva et al. 1995, 2002b). Oxytocin, although not commonly used, is typically positive in smooth muscle tumors but negative in endometrial stromal tumors (Loddenkemper et al. 2003). Transgelin, a new smooth muscle marker, has been recently shown not to be expressed in endometrial stromal tumors and may also be helpful in this differential diagnosis (Tawfik et al. 2014).

Caution should be exercised when immunohistochemistry is employed to distinguish between highly cellular leiomyomas and endometrial stromal tumors since zones of smooth muscle differentiation in endometrial stromal neoplasms, when present, typically express smooth muscle markers. This finding, by itself, would not be informative about the presence of a stromal neoplasm.

Classification of such tumors would be based on the presence or absence of a stromal component, which can be ascertained by correlating immunohistochemical results with morphology. Thus, as no single marker is entirely sensitive or specific, a panel of immunostains including CD10 and at least two smooth muscle markers (desmin and h-caldesmon are most commonly used) is useful in distinguishing between endometrial stromal tumors and smooth muscle neoplasms. Rarely, cellular IVL may be confused with a low-grade endometrial stromal sarcoma, as both share dense cellularity and intravascular growth, even more if the latter is associated with a highly cellular leiomyoma. However, IVL is characterized by fascicular growth of spindle cells, large, thick blood vessels, as well as cleft-like spaces (as seen in typical leiomyomas), and sometimes a subendothelial proliferation of spindle cells "colonizing" the walls of the veins, pointing to the origin of the neoplasm (Clement et al. 1988; Oliva 2014). Adenomyosis, which can be gland-poor or present in vascular spaces, may raise concern for a typical endometrial stromal sarcoma. In such instances, no mass is noted, adjacent adenomyosis with atrophic stroma is present, and no areas of typical endometrial stromal neoplasia are identified (Goldblum et al. 1995).

Cellular endometrial polyps, when fragmented and present in a curetting, may also raise concern for an endometrial stromal tumor. In general, the fragments composed of stroma only contain stromal cells, with an inactive-to-atrophic "compacted" appearance and without mitotic activity. Furthermore, they lack the arteriolar-type vessels characteristic of endometrial stromal tumors, and instead display medium-to-large vessels in at least some of the fragments. Other fragments may show show similar stroma admixed with inactive endometrial glands (Oliva et al. 2000). One study found that in a curettage, most endometrial stromal tumors were represented by fragments containing only or predominantly endometrial stroma measuring >5 mm (Stemme et al. 2014). As mentioned previously, one cannot confidently distinguish between endometrial stromal nodule and low-grade endometrial stromal sarcoma in this setting since it is impossible to visualize the interface between tumor and myometrium.

Extensive sex cord-like differentiation may raise the possibility of a uterine tumor resembling ovarian sex cord stromal tumor (Clement and Scully 1976), especially in a curettage specimen. The presence of any endometrial stromal component excludes that possibility. Thus, a diagnosis of UTROSCT cannot be established in curettage specimens, as the tumor is not fully sampled (Baker and Oliva 2007; Hoang et al. 2018; Nucci 2016; Oliva et al. 2000). Uterine tumors resembling sex cord tumors have been reported to be more frequently positive for markers of sex cord differentiation including calretinin (most common), CD99, Melan-A, and inhibin, when compared to endometrial stromal tumors with sex cord-like differentiation (Irving et al. 2006). Another potentially helpful marker is FOXL2, as UTROSCT may express this marker in contrast to endometrial stromal tumors with sex cord-like differentiation which in one study were all negative (Stewart et al. 2016b). Sex cord-like areas in curettings may rarely raise the diagnosis of an epithelioid smooth muscle tumor with nests, cords, or trabeculae, or an endometrioid carcinoma with sertoliform morphology (Eichhorn et al. 1996; Liang et al. 2007). Furthermore, the immunohistochemical profile of all these tumors may partially overlap. However, the finding of a spindle component with strong desmin and caldesmon staining +/− EMA positivity but negative staining for sex cord markers supports a diagnosis of smooth muscle tumor. Conventional areas of endometrial stromal neoplasia are negative for desmin and caldesmon, and areas with sex cord-like differentiation are positive for at least one sex cord marker, usually calretinin or CD99 (Irving et al. 2006; Oliva 2016; Portugal and Oliva 2009). Endometrial carcinomas should only be positive for epithelial markers including EMA, with rare exceptions being positive for inhibin (Liang et al. 2007). YWHAE-FAM22 high-grade endometrial stromal sarcoma may enter in the differential diagnosis of

sex cord-like areas (or endometrial stromal sarcoma with epithelioid morphology), as cells are rounded and grow in nests; however, there is uniform cytologic atypia as well as brisk mitotic activity and tumor cells are cyclin D1-positive but CD10, ER, and PR negative (Lee et al. 2012a).

Endometrial stromal tumors with glandular differentiation should be distinguished from florid adenomyosis, which can be intravascular. As mentioned above, the latter does not form a mass lesion but at most an irregular thickening within the myometrium containing atrophic nests, in contrast to the expansile and proliferative appearance of endometrial stromal sarcomas. Florid adenomyosis is almost always associated with other more typical areas of adenomyosis (Goldblum et al. 1995; Hirschowitz et al. 2013). Other entities in the differential diagnosis include low-grade müllerian adenosarcoma (if glands are benign) or rarely carcinosarcoma (if glands are malignant). Adenosarcoma can be distinguished from endometrial stromal tumors by the typical condensation of low-grade malignant stroma, phyllodes architecture, and variety of epithelia, and carcinosarcoma by glands and stroma showing high-grade cytologic features (Clement and Scully 1992).

Fibroblastic and myxoid endometrial stromal tumors are most often misclassified as myxoid or edematous smooth muscle tumors. The latter displays foci of cells with elongated blunted nuclei growing in fascicles, as well as large, thick blood vessels as the predominant vascular component (Burch and Tavassoli 2011). Smooth muscle tumors are generally positive for desmin and caldesmon, but staining is not infrequently focal/weak or absent, especially for caldesmon, limiting the utility of immunohistochemistry in this differential diagnosis (Parra-Herran et al. 2016). p53 positivity may favor a malignant smooth muscle tumor, as endometrial stromal tumors are typically negative (Kurihara et al. 2008; Schaefer et al. 2017). Smooth muscle actin is commonly positive in endometrial stromal tumors and thus not helpful in this differential diagnosis. Neurofibromas and malignant nerve sheath tumors are rare in the uterus. The former typically occur in the setting of neurofibromatosis and are characterized by S100 positive cells with wavy nuclei set in a fibromyxoid background lacking areas of conventional endometrial stromal neoplasia (Gersell and Fulling 1989; Gomez-Laencina et al. 2012). Although malignant nerve sheath tumors have been reported only in the cervix, they may vaguely resemble endometrial stromal sarcomas, including predominantly fibroblastic sarcomas, and may be a diagnostic consideration in curettage specimens or tumors arising in the low uterine segment. Furthermore, they can have prominent small vessels. They are often positive for SOX10 and S100, and CD34 if fibroblastic (Keel et al. 1998; Mills et al. 2011).

Rarely, multifocal myxoid change within the myometrium may be considered in the differential diagnosis of a myxoid endometrial stromal sarcoma due to multifocal distribution of typically well-demarcated myxoid CD10-positive nodules. The nodules are paucicellular, containing uniform cells with a fibroblastic morphology. In contrast to endometrial stromal tumors, no areas of conventional endometrial stromal neoplasia are identified and cells are also CD34-positive. This finding has been associated with neurofibromatosis type I (Pugh et al. 2012). Myxomas are exceedingly rare in the uterus, but on microscopic examination may be extremely difficult to distinguish from a myxoid endometrial stromal tumor. However, they are centered in the myometrium, lack vasculature and typical areas of endometrial stromal neoplasia, and are associated with the Carney syndrome (Barlow et al. 1983).

Clinical Behavior and Treatment

Most patients with low-grade endometrial stromal sarcoma present with stage I tumors (~80%), while ~20% have metastatic disease at the time of diagnosis (Chan et al. 2008; Felix et al. 2013). These tumors are typically characterized by a slow, indolent course, with an overall 5-year disease-specific survival of >90% for all stages, despite approximately one-third to one-half of patients suffering one or more recurrences.

Ten-year survivals are at least 75% (Abeler et al. 2009). Patients with stage III and IV tumors have been reported to develop recurrences within 9 months and are associated with significantly decreased survivals (Chang et al. 1990), although scrutiny of these data suggest many of the high-stage tumors reported would now be considered "high-grade endometrial stromal sarcomas" lacking pleomorphic nuclei. Extrauterine disease is widely distributed, affecting one or more of the following: pelvis, lymph nodes, abdomen, lung, or bone (Chang et al. 1990; Fukunaga and Endo 1996; Mansi et al. 1990). Though distant metastases are uncommon, lung is the most affected site (7–28%) (Aubry et al. 2002). Over time, the morphologic appearance of the tumor may change in accordance with an increase in aggressiveness, and the patient may be misdiagnosed with a different tumor.

Treatment consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy, as risk of recurrence is higher if only hysterectomy is performed (Feng et al. 2013a; Li et al. 2008; Nordal et al. 1996). Omentectomy or lymph node dissection does not seem to influence survival in patients with early-stage tumors (Chan et al. 2008; Shah et al. 2008). The frequency of lymph node metastases ranges from 0% to 16% (Amant et al. 2007; Feng et al. 2013a; Signorelli et al. 2010) and is frequently associated with gross extrauterine disease, extensive myoinvasion, and lymphovascular invasion (Dos Santos et al. 2011). Radiation therapy may be helpful to control local recurrences but does not seem to improve overall survival (Barney et al. 2009; Gadducci et al. 1996b; Leath et al. 2007). Hormonal therapy is also utilized, including GnRH analogs, progestins, and aromatase inhibitors, especially in metastatic/recurrent disease or patients that want to preserve fertility (Gadducci et al. 2008; Reich and Regauer 2004, 2007). Evaluation of ER and PR status is recommended by some at the time of initial diagnosis and recurrence, as loss in the latter may be indicative of more aggressive behavior (Gadducci et al. 2008).

Besides stage, the impact of other prognostic parameters on survival in endometrial stromal sarcoma is controversial, especially in patients with stage I tumors. Some studies have shown that older age (>50 years) (Akahira et al. 2006; Bodner et al. 2001; Nordal et al. 1996), black race (Chan et al. 2008; Leath et al. 2007), multiparity (Albrektsen et al. 2009), and postmenopausal status (Chauveinc et al. 1999; Nordal et al. 1996; Park et al. 2008) were associated with worse outcome, but others have contradicted these findings (Albrektsen et al. 2009; Brooks et al. 2004; Koivisto-Korander et al. 2008). Among pathologic factors, the prognostic significance of mitotic activity and tumor cell necrosis have been debated. In a study of 85 endometrial stromal sarcomas in a cohort of 419 uterine sarcomas, mitotic activity was found to be an independent prognostic factor in stage I tumors, with tumor cell necrosis and > 10 MF/10 HPF being associated with worse outcomes, while another study postulated that high proliferation measured by mitotic index, Ki67 or PHH3, may be predictive of recurrences (Feng et al. 2013c, 2013d). On the contrary, in the largest study of these tumors, mitotic activity had no predictive value in stage I tumors by multivariate analysis but was associated with poorer survival in patients with extrauterine disease at time of diagnosis (Chang et al. 1990). Tumor cell necrosis, a well-known defining feature of leiomyosarcomas, has also been associated with poor prognosis in endometrial stromal sarcomas (Abeler et al. 2009). Patients with sarcomas without necrosis had a 96% 5-year overall survival rate in contrast to 69% for those with tumors with necrosis. In another study, tumors with inconspicuous or absent necrosis had 5- and 10-year survival rates of ~90% and 80%, compared with ~45% in those with extensive necrosis (Feng et al. 2013b). However, the largest series to date did not confirm that association (Chang et al. 1990). The prognostic influence of tumor size, lymphovascular invasion, hormonal status, and ploidy is unclear (Chew and Oliva 2010). Many of the studies cited here were performed before recognition of specific types of high-grade endometrial stromal sarcomas that lack pleomorphic nuclei; it is therefore possible that these data

unintentionally exaggerated associations between both mitotic activity/necrosis and clinical outcomes in low-grade endometrial stromal sarcoma.

High-Grade Endometrial Stromal Sarcoma

Two well-defined categories of high-grade endometrial stromal sarcomas are recognized. One was described after the most recent WHO classification publication, and both are morphologically, immunohistochemically, and molecularly distinct from typical low-grade endometrial stromal tumors and each other (Oliva et al. 2014). However, a third category should be recognized, in which sarcomas, not otherwise specified, may arise in a background of low-grade endometrial stromal sarcoma.

YWHAE-FAM22 (YWHAE-NUTM2) High-Grade Endometrial Stromal Sarcoma

YWHAE-FAM22 high-grade endometrial stromal sarcomas are seen in patients across a wide age range (25–70 years), often presenting with abnormal vaginal bleeding or enlarged uterus/pelvic mass at physical exam. On gross examination, they are often large, bulky tumors (median ~8 cm), with a white, fleshy cut surface and frequent areas of necrosis and hemorrhage (Lee et al. 2012b).

On microscopic examination, they are characterized by a permeative growth within the myometrium and myometrial veins, as seen in low-grade endometrial stromal sarcomas. On high-power examination, tumors are hypercellular and display round cells with scant to moderately abundant cytoplasm, round to angulated nuclei (at least four times larger than lymphocyte nuclei), and finely granular-to-vesicular chromatin without visible nucleoli and associated brisk mitotic activity (typically >10 MF/10 HPF, but often >20–30 MF/10 HPF). Cells are arranged in vague nests or as a diffuse growth associated with a delicate sinusoidal vasculature (Fig. 61). A focal pseudopapillary, cord-like or rosette-like morphology has been reported (Amant et al. 2011; Lee et al. 2012b). Approximately 50% of these tumors display a second component characterized in most instances by a low-grade spindle morphology with or without associated myxoid background, as typically seen in low-grade fibromyxoid endometrial stromal sarcomas. This component is hypocellular and displays oval-to-spindle cells with bland cytologic features embedded in a delicate collagenous or myxoid background but with the arteriolar vasculature that characterizes typical endometrial stromal tumors (Oliva et al. 1999; Yilmaz et al. 2002). Rarely, YWHAE-FAM22 high-grade endometrial stromal sarcomas have evolved from a conventional low-grade endometrial stromal sarcoma at a metastatic site (Aisagbonhi et al. 2017).

The high-grade component of these tumors is typically strongly and diffusely positive for cyclin D1 (>70% of cells) (Fig. 62a), and in contrast to low-grade tumors, negative for CD10 (Fig. 62b). ER and PR may be positive, but only minimally (Lee et al. 2012a). They also express BCOR and c-kit (without associated mutations) but are negative for DOG1 (Chiang et al. 2017a; Lee et al. 2014). BCOR is a more sensitive marker than cyclin D1 in the detection of these tumors (Chiang et al. 2017a). In contrast, the low-grade component expresses CD10, ER, and PR but no or very little cyclin D1. They may show focal and weak staining with IFITM1 (Busca et al. 2017; Parra-Herran et al. 2014). These tumors display *t*(10;17)(q22;p13) rearrangements associated with *YWHAE-FAM22* (also known as *YWHAE-NUTM2*) fusions that can be detected by FISH or RT-PCR. FISH appears to be more sensitive, with a cutoff of at least 20–30% positive cells, though lower detection may still be indicative of this translocation (Croce et al. 2013; Kruse et al. 2014a). An identical fusion has been reported in clear cell sarcoma of the kidney (Punnett et al. 1989; Rakheja et al. 2004). This translocation has been rarely detected in endometrial stromal tumors with typical low-grade or variant morphologic features.

Although this tumor has a very characteristic morphologic appearance, diagnostic

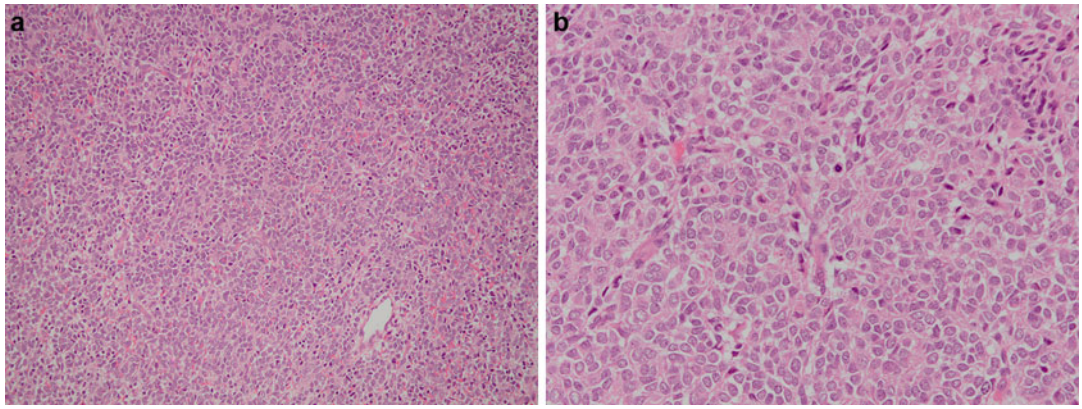

Fig. 61 YWHAE-FAM22 high-grade endometrial stromal sarcoma. (**a**) The tumor is hypercellular and characterized by a diffuse or nested growth of small uniform cells. (**b**) Cells are round with scant cytoplasm, contain round to angulated nuclei without visible nucleoli, and display associated brisk mitotic activity. These tumors may contain a component of low-grade endometrial stromal sarcoma

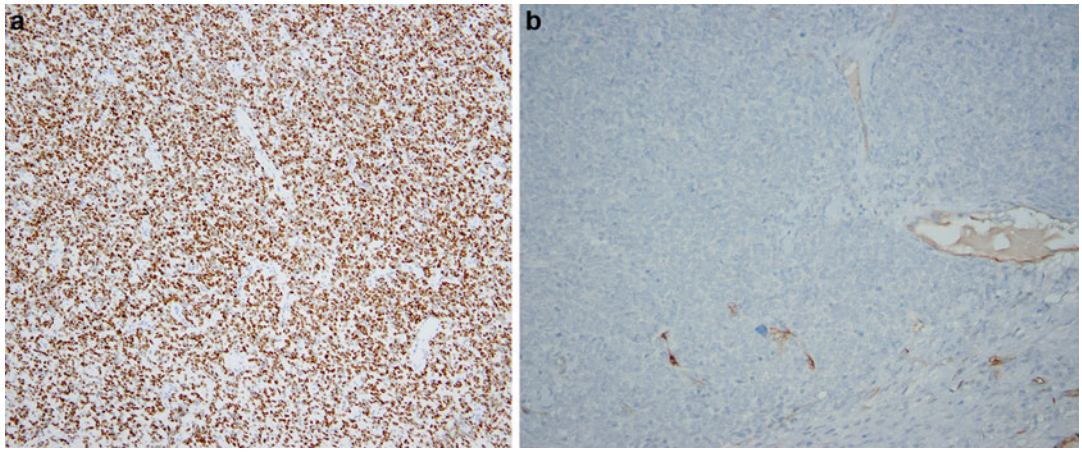

Fig. 62 YWHAE-FAM22 high-grade endometrial stromal sarcoma. Tumor cells are diffusely positive for cyclin D1 (**a**) but negative for CD10 (**b**), in contrast to typical endometrial stromal tumors

considerations, especially in biopsy specimens, include undifferentiated/dedifferentiated carcinoma, epithelioid leiomyosarcoma, primitive neuroectodermal tumor (PNET), undifferentiated uterine sarcoma, gastrointestinal tumor (if the biopsy is of an extrauterine mass), or metastases. Undifferentiated/dedifferentiated carcinomas are composed of monomorphous noncohesive medium-sized round cells that may show strong and diffuse cyclin D1 staining and are typically negative for PAX8 and EMA, features that overlap with YWHAE-NUTM2 endometrial stromal sarcoma (Shah and McCluggage 2015), especially if no associated low-grade carcinoma is present. Undifferentiated carcinomas have a striking diffuse growth and stain for keratin cocktail and keratin 8/18, and half display concurrent loss of MLH1 and PMS2 or loss of E-cadherin and CD44 (Ramalingam et al. 2016). Epithelioid leiomyosarcoma may display round cells and rarely can be cyclin D1 and BCOR positive (Chiang et al. 2017a; Lee et al. 2012a). However, they also commonly display an overtly malignant spindle cell component, as

well as positivity for smooth muscle markers including desmin and h-caldesmon, and are often keratin and EMA positive.

PNETs are exceedingly rare in the uterus, but because they are highly cellular and may display rosettes, they may enter in the differential diagnosis of YWHAE-NUTM2 endometrial stromal sarcomas. Furthermore, the latter can, on occasion, express CD99, a common marker in PNETs. However, PNET cells lack cytoplasm and, if of central type, half express GFAP, while those of peripheral type are associated with *EWSR1* rearrangement (Chiang et al. 2017a; Euscher et al. 2008). Rarer tumors that have morphologic and immunophenotypic features of Ewing sarcoma/peripheral PNET, but lack *EWSR1* rearrangement, may enter in the differential diagnosis, although they have not been reported yet in the uterus; these harbor less common alterations affecting *FUS, BCOR, CCNB3, CIC*, or *DUX4* (Hung et al. 2016). Undifferentiated sarcomas may rarely enter in the differential diagnosis as they may be extensively positive for cyclin D1. However, they also show extensive and strong CD10 staining and more importantly typically display marked pleomorphism as well as destructive myometrial invasion, in contrast to YWHAE-NUTM2 endometrial stromal sarcomas (Oliva et al. 2014; Sciallis et al. 2014). Epithelioid gastrointestinal stromal tumors and YWHAE-NUTM2 endometrial stromal sarcomas share expression of c-kit, but the latter typically involves primarily the uterus, lacks c-kit mutations, and does not express *DOG1* (Miettinen and Lasota 2011; Novelli et al. 2010; Terada 2009).

These tumors are detected at more advanced stages (stage II or III) when compared to low-grade endometrial stromal sarcomas, and patients more often develop recurrences, usually early, having an intermediate behavior between low-grade endometrial stromal sarcomas and undifferentiated uterine sarcomas (Kruse et al. 2014a; Lee et al. 2012b). Standard treatment is hysterectomy followed by chemotherapy with or without radiation. Chemotherapy with anthracycline-based drugs led to complete radiologic response in a small series (Hemming et al. 2017). YWHAE-NUTM2 endometrial stromal sarcoma may not be present in the primary tumor but in recurrences or metastases (Aisagbonhi et al. 2017). Although immunohistochemical or molecular tools may allow detection of low-grade tumors with *YWHAE-NUTM2* fusion, it is unknown which tumors will evolve to a high-grade endometrial stromal sarcoma.

ZC3H7B-BCOR High-grade Endometrial Stromal Sarcoma

ZC3H7B-BCOR endometrial stromal sarcoma is a newly described subtype of high-grade endometrial stromal sarcoma that closely mimics the appearance of myxoid leiomyosarcoma. Although its frequency is reported as low, it may in fact be higher, as in the past these tumors were frequently misdiagnosed as leiomyosarcoma (Hoang et al. 2017; Lewis et al. 2018; Marino-Enriquez et al. 2018).

In the only series reported to date, typical tumors occur within a wide age range (28–71 years), but most frequently in the fifth decade. A subgroup characterized by *BCOR* internal tandem duplications (*BCOR*-ITD) occurs in younger patients (18–32 years) (Marino-Enriquez et al. 2018). Patients present with nonspecific symptoms including vaginal bleeding and/or pelvic mass, and not infrequently have extrauterine disease at initial diagnosis (Hoang et al. 2017; Lewis et al. 2018).

On gross examination, these tumors are often large (mean 10 cm), polypoid, and centered in the endometrium, but can be myometrial-based. They have a solid, soft, fleshy-to-rubbery, tan-to-yellow-to-pink cut surface.

On low-power microscopic examination, they typically show a tongue-like, broad front, or destructive (least common) pattern of invasion, or a combination thereof. Tumors tend to be uniformly cellular growing in haphazard fascicles of spindle cells without overt pleomorphism (Fig. 63). Cells have scant-to-relatively-abundant gray-to-eosinophilic cytoplasm and oval-to-spindle nuclei with inconspicuous nucleoli and evenly distributed chromatin. BCOR-ITD tumors often have a component

of round epithelioid cells admixed with the spindle cells. Mitotic activity often exceeds 15 MF/10 HPF. Vascularity, when prominent, is characterized by small arterioles without striking perivascular whorling of tumor cells but may include large and/or hemangiopericytoma-like vessels. The background stroma is either myxoid, including variably sized pools of basophilic material, or collagenous; collagen plaques are commonly seen (Fig. 63). Areas of necrosis and lymphovascular invasion are frequent (Hoang et al. 2017; Lewis et al. 2018). In contrast to YWHAE-NUTMT2 high-grade endometrial stromal sarcomas, these tumors are not associated with a conventional or variant component of endometrial stromal sarcoma.

The immunohistochemical profile of typical ZC3H7B-BCOR tumors and those with BCOR-ITD closely overlaps, except for CD10 expression, which is typically positive, often with a diffuse and strong pattern of staining in typical ZC3H7B-BCOR tumors but negative or only focally positive staining in BCOR-ITD tumors (Hoang et al. 2017; Lewis et al. 2018; Marino-Enriquez et al. 2018). ER and PR are variably positive. Cyclin D1 is strong and diffuse in most tumors, and BCOR is also frequently positive (Fig. 64b), although staining ranges from weak

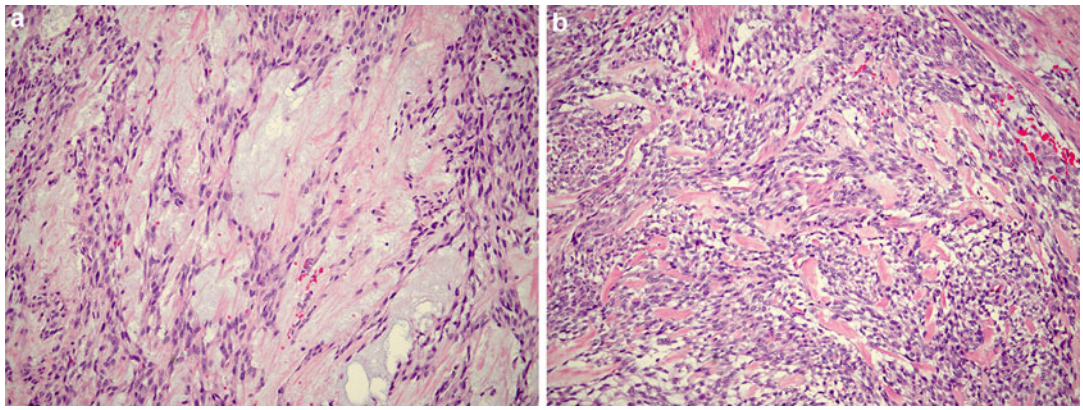

Fig. 63 ZC3H7B-BCOR high-grade endometrial stromal sarcoma. (**a**) The tumor may have a vague fascicular growth of tumor cells associated with prominent myxoid background, mimicking a myxoid leiomyosarcoma. (**b**) Other areas contain spindle cells associated with collagen plaques, as seen in typical endometrial stromal tumors

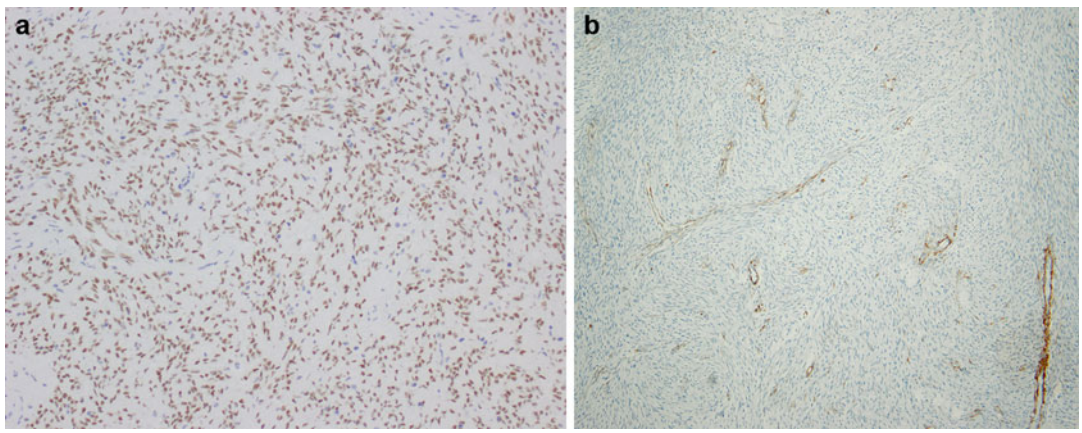

Fig. 64 ZC3H7B-BCOR high-grade endometrial stromal sarcoma. The tumor is frequently positive for BCOR (**a**) and cyclin D1, and negative for caldesmon (**b**), in contrast to myxoid leiomyosarcomas

to strong. There tends to be concordant positivity between cyclin D1 and BCOR (Chiang et al. 2017a; Hoang et al. 2017; Lewis et al. 2018). Among smooth muscle markers, actin is more frequently expressed (typically focally), while desmin and caldesmon are almost always negative (Fig. 64a). These tumors are characterized by *ZC3H7B-BCOR* fusions that result from the t(X;22)(p11q13) rearrangement, which can be detected by FISH or PCR. A minority of tumors show internal tandem duplications (ITDs) involving exon 15 of *BCOR* (Hoang et al. 2017; Lewis et al. 2018; Marino-Enriquez et al. 2018).

Myxoid leiomyosarcoma is the most common entity in the differential diagnosis of these high-grade endometrial stromal sarcomas and in the past were likely diagnosed as such. Distinguishing features of ZC3H7B-BCOR stromal sarcomas include lack of well-formed fascicles, cells with cigar-shaped nuclei, and expression of desmin and caldesmon. In one study, only 1 of 19 leiomyosarcomas was positive for BCOR (Chiang et al. 2017a), while in another study only 1 of 80 such tumors was diffusely positive for cyclin D1 (Lee et al. 2012a). Low-grade endometrial stromal sarcoma may enter in the differential diagnosis, as both share a tongue-like pattern of myometrial invasion as well as cells with uniform cytologic features, collagen bands, and in some instances CD10, ER, and PR positivity. However, BCOR-ITD and typical ZC3H7B-BCOR high-grade endometrial stromal sarcomas lack the features reminiscent of proliferative phase endometrium, including the characteristic vasculature, and display brisk mitotic activity. Furthermore, low-grade endometrial stromal sarcomas express CD10, ER, and PR, but not BCOR or cyclin D1 (with rare exceptions; staining is only focal and weak) (Chiang et al. 2017a). Rarely, adenosarcoma with sarcomatous overgrowth and IMT may enter in the differential diagnosis of these tumors, as they can also display a myxoid background. However, the former typically has characteristic areas of low-grade müllerian adenosarcoma, and thus far has not been associated with BCOR genetic alterations (although immunohistochemical expression of BCOR can occur) (Howitt et al. 2015b), while the latter contains an inflammatory infiltrate and overexpresses ALK as a result of genetic rearrangements. Finally, undifferentiated uterine sarcoma may be considered in the differential diagnosis, and in fact, two out of three BCOR-ITD high-grade endometrial stromal sarcomas were originally diagnosed as undifferentiated uterine sarcomas (Marino-Enriquez et al. 2018). The latter is in general more pleomorphic, without associated collagen plaques, and typically has a destructive invasion pattern.

Hysterectomy and bilateral salpingo-oophorectomy with adjuvant chemotherapy is standard treatment. Although experience with these tumors is limited, patients with ZC3H7B-BCOR high-grade endometrial stromal sarcomas have a prognosis that parallels that of patients with YWHAE-NUTM2 high-grade sarcomas, as both are associated with higher stage at presentation (including lymph node metastases) and frequent recurrences and metastases (Lewis et al. 2018; Marino-Enriquez et al. 2018).

Other High-Grade Endometrial Stromal Sarcomas

Rarely, a high-grade pleomorphic or heterologous sarcoma may be seen in association with a low-grade endometrial stromal sarcoma, in which instance a diagnosis of high-grade endometrial stromal sarcoma can be rendered (Amant et al. 2006; Cheung et al. 1996; Kurihara et al. 2008; Malpica et al. 2006; McCluggage and Young 2008; Ohta et al. 2010; Sciallis et al. 2014); however, some investigators designate these tumors as dedifferentiated endometrial stromal sarcoma. Although many monomorphic undifferentiated uterine sarcomas are likely to represent high-grade endometrial stromal sarcoma (Sciallis et al. 2014), the current WHO maintains the "undifferentiated uterine sarcoma" nomenclature (Oliva et al. 2014). Patients often present with vaginal bleeding or a uterine mass and have extrauterine disease at the time of diagnosis. The high-grade component may show a permeative or destructive pattern of invasion. Cells may be pleomorphic or uniform, with epithelioid or spindle

morphology, variable amounts of cytoplasm, and hyperchromatic and irregular nuclei with prominent nucleoli and high mitotic index, including atypical forms. The cells grow in a diffuse manner and are associated with extensive areas of necrosis and, rarely, heterologous differentiation (rhabdomyosarcoma) (Kurihara et al. 2008; Sciallis et al. 2014). Areas of conventional low-grade endometrial stromal sarcoma are present in variable extent. By immunohistochemistry, CD10, ER, and PR are often negative in the high-grade component when pleomorphic but typically positive in the low-grade component (Malpica et al. 2006; Sciallis et al. 2014). Staining for cyclin D1 may be focally positive or there may be p53 overexpression (Jung et al. 2008; Kurihara et al. 2008, 2010; Ohta et al. 2010). They may express AE1/3 and CAM 5.2 (Rahimi et al. 2018). Fusion of *JAZF1* and *JJAZ1* genes has been identified in these tumors on rare occasions (Koontz et al. 2001; Kurihara et al. 2008).

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcoma is an extremely rare and heterogeneous category of malignant mesenchymal tumors, defined by the most recent WHO classification as neoplasms that arise in the endometrium or myometrium with high-grade cytologic features lacking any resemblance to proliferative-phase endometrial stroma and with no specific differentiation. These tumors are difficult to classify, and thus, their diagnosis is one of exclusion after other possibilities, including high-grade endometrial stromal sarcoma, undifferentiated/dedifferentiated carcinoma, adenosarcoma with sarcomatous overgrowth, carcinosarcoma (MMMT) with minimal epithelial component, or dedifferentiated leiomyosarcoma have been ruled out (Oliva et al. 2014). Before publication of the recent WHO classification, Kurihara and colleagues analyzed a group of undifferentiated endometrial sarcomas and divided them into uniform and pleomorphic types (Kurihara et al. 2008). In the former group, some tumors were ER- and PR-positive and had mutations in β-catenin but lacked p53 mutations and showed a component of low-grade endometrial stromal sarcoma, while others were ER- and PR-negative and diffusely cyclin D1-positive. Thus, these authors recognized that most monomorphic undifferentiated sarcomas could be categorized into immunohistochemically defined entities that likely correspond to YWHAE- and BCOR-rearranged high-grade endometrial stromal sarcomas. Tumors in the third, pleomorphic category were typically ER-, PR-, and β-catenin-negative but often expressed p53; this very small group of tumours likely represents true undifferentiated sarcomas.

Undifferentiated uterine sarcomas typically occur in postmenopausal women that present with vaginal bleeding and signs and symptoms related to a rapidly growing mass and/or metastatic disease (Kurihara et al. 2008; Prat and Mbatani 2015; Tanner et al. 2012).

On gross examination, these tumors are typically large fleshy masses that may involve the endometrium and/or myometrium, some being polypoid; they are often associated with extensive areas of hemorrhage and necrosis (Fig. 65). On microscopic examination, pleomorphic undifferentiated uterine sarcomas are characterized by a destructive pattern of invasion. Like other high-grade sarcomas (Fig. 66), the spindle or epithelioid tumor cells often grow in sheets or fascicles and display marked cytologic atypia, including multinucleation and brisk mitotic activity with atypical mitoses (Fig. 67). Necrosis (Fig. 68) and

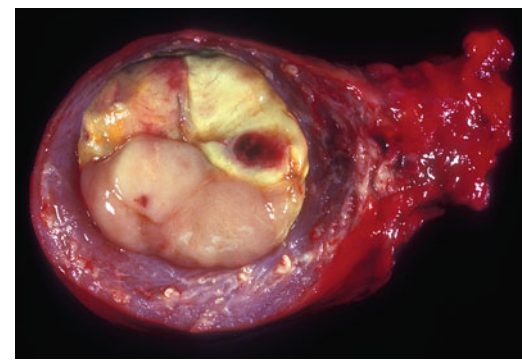

Fig. 65 Undifferentiated uterine sarcoma. The tumor is polypoid, fills the uterine cavity, and displays a white, fleshy cut surface with extensive areas of necrosis

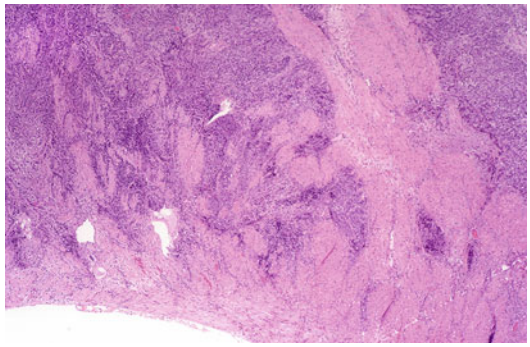

Fig. 66 Undifferentiated uterine sarcoma. The invasion pattern is destructive, in contrast to the tongue-like permeative invasion seen in endometrial stromal sarcoma

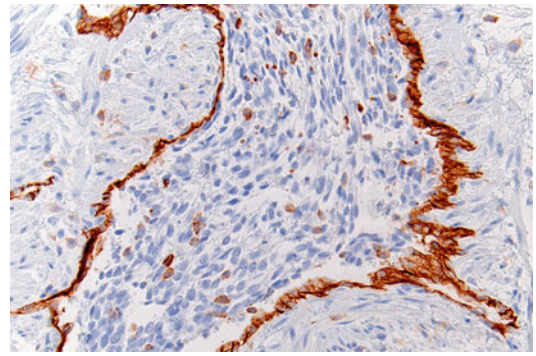

Fig. 69 Undifferentiated uterine sarcoma. These are very aggressive tumors that are frequently associated with lymphovascular invasion as revealed by a CD31 stain

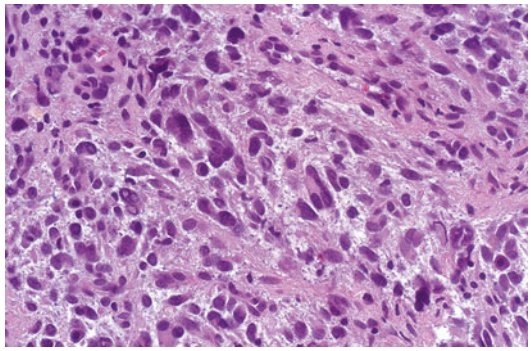

Fig. 67 Undifferentiated uterine sarcoma. The tumor is composed of pleomorphic hyperchromatic cells including multinucleated cells. This is a diagnosis of exclusion

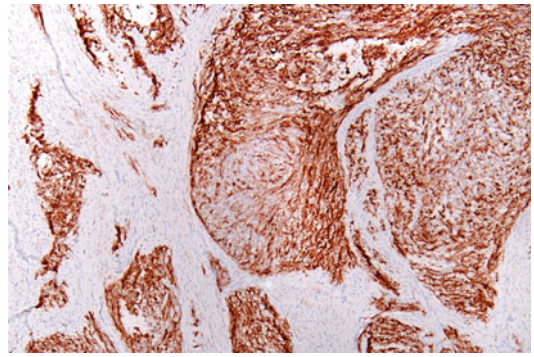

Fig. 70 Undifferentiated uterine sarcoma. The tumor cells may show extensive staining for CD10, but they are often negative for ER and PR

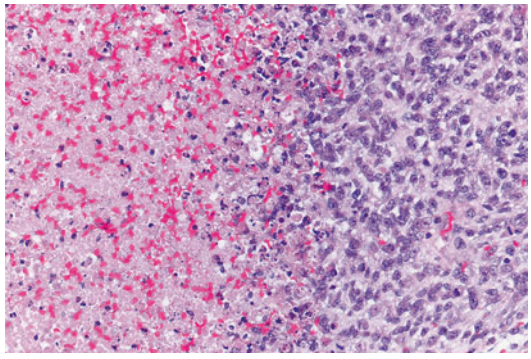

Fig. 68 Undifferentiated uterine sarcoma. These tumors often contain extensive areas of tumor cell necrosis

lymphovascular invasion are common (Fig. 69) (Bartosch et al. 2010; Evans 1982).

These tumors may show variable staining for CD10 (Fig. 70), but pleomorphic sarcomas are typically ER- and PR-negative (Bartosch et al. 2010; Gremel et al. 2015; Kurihara et al. 2010). Cyclin D1 may be variably expressed. Pleomorphic undifferentiated sarcomas may also express p16, p53 (Gremel et al. 2015); other immunohistochemical markers including keratin, smooth muscle actin, or desmin may be positive, but only focally (Bartosch et al. 2010; Kurihara et al. 2008). Gene expression

studies have found that pleomorphic undifferentiated uterine sarcomas harbor more chromosomal alterations and complex karyotypes than typical endometrial stromal sarcomas. Data suggest that progression from typical endometrial stromal sarcomas to undifferentiated sarcomas is unlikely although not impossible (Flicker et al. 2015; Gil-Benso et al. 1999; Halbwedl et al. 2005; Micci et al. 2016). *JAZF1-SUZ12* rearrangements have rarely been detected in undifferentiated uterine sarcomas (Koontz et al. 2001), particularly monomorphic sarcomas, but a recent study failed to identify this rearrangement (Jakate et al. 2013). Another study identified five copy number alterations encompassing cancer-related genes (*EZR, CDH1, RB1, TP53*, and *PRKAR1A*) accompanied by corresponding expression changes in undifferentiated uterine sarcomas, suggesting that they may have some impact on the development of these tumors (Choi et al. 2015).

As this is a diagnosis of extensive sampling, immunohistochemistry and, if required, analysis for stromal sarcoma-related fusions are strongly recommended to exclude entities in the differential diagnosis. CD10 expression is insufficient evidence for a diagnosis of undifferentiated uterine sarcoma, as this marker is positive in most tumors (epithelial, mesenchymal, and mixed) that occur in the uterus. Very recently, a very small number of undifferentiated uterine sarcomas have been reported to display a rhabdoid morphology with loss of expression of SMARCA4 (Kolin et al. 2018).

Overall, these tumors are associated with poor patient outcomes, even among those diagnosed with stage I tumors, despite aggressive treatment; a large number of patients have disease outside the uterus at the time of diagnosis (Evans 1982; Kurihara et al. 2008). Survivals for patients with pleomorphic undifferentiated sarcomas appear to have worse clinical outcomes compared to those with monomorphic tumors. Five-year survival rates of 70%, 43%, and 23% have been reported for localized, regional, and distant disease (American Cancer Society 2017). A recent study stratified the prognosis of undifferentiated uterine sarcomas based on mitotic index, hormone receptor expression, and *YWHAE-FAM22* translocation status. Tumors with >25 MF/10 HPF lacking ER, PR, and *YWHAE-FAM22* translocation had poorer prognoses (Gremel et al. 2015).

Mixed Epithelial–Mesenchymal Tumors

Mixed epithelial–mesenchymal tumors contain both epithelial and mesenchymal elements. The mixed epithelial–mesenchymal tumor group as listed in the 2014 WHO classification of tumors of the uterine corpus (Table 1) includes adenomyoma, atypical polypoid adenomyoma (APA), adenofibroma, adenosarcoma, and carcinosarcoma (also known MMMT) (Kurman et al. 2014). APA typically originates in the endometrium, and carcinosarcoma is considered to be a special type of sarcomatoid or metaplastic endometrial carcinoma, so in this book they are discussed in the chapters on benign diseases of the endometrium and endometrial carcinoma, respectively.

Adenomyosis and Adenomyoma

Adenomyosis is a common condition, detected in 15–30% of hysterectomy specimens. It is characterized by the presence of endometrial glands and stroma within the myometrium. Adenomyomas are uncommon tumor-like masses composed of endometrial glands, endometrial stroma, and smooth muscle, with the latter generally predominating. They differ from adenomyosis mainly in that they are circumscribed nodular masses.

Clinical Features

Patients are typically pre- or perimenopausal women who present with abnormal bleeding and dysmenorrhea (Gordts et al. 2018). Younger patients may present due to impaired

reproduction, and up to a third of patients with adenomyosis are asymptomatic. Symptoms tend to be more severe in women with deep myometrial involvement. The uterus is typically enlarged and may harbor other lesions associated with hyperestrinism, such as leiomyomas, pelvic endometriosis, and endometrial polyps. Adenomyosis is usually most extensive in the posterior wall, which may be thickened. A clinical diagnosis of adenomyosis can often be confirmed by imaging studies such as transvaginal ultrasonography or MRI.

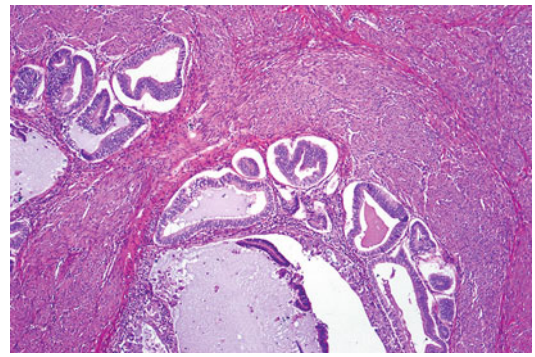

Fig. 71 Adenomyosis. The periphery of this focus of adenomyosis containing endometrial hyperplasia is relatively lacking in endometrial stroma. This focus can be recognized as adenomyosis because of its lobular shape and the circumferential smooth muscle hypertrophy that surrounds it

Pathologic Findings

On gross examination, the cut surface of the myometrium is trabeculated and contains hemorrhagic foci, but a distinct tumor nodule is not present. Small blood-filled cysts may be noted.

Adenomyosis is a condition in which rounded or irregular foci of endometrial stroma and glands are present in the myometrium, usually surrounded by bundles of hypertrophic myometrial smooth muscle (Fig. 71). Cystic or blood-filled endometrial glands are sometimes present in foci of adenomyosis, accounting for the small blood-filled cysts that are seen on gross examination in some cases. The lower border of the endometrium is irregular and dips into the superficial myometrium. To avoid misclassifying a normal histologic finding as adenomyosis, the diagnosis is made only when the distance between the lower border of the endometrium and the adenomyosis exceeds the diameter of a 100x microscopic field (about 2 mm), an admittedly arbitrary measurement (Bergeron et al. 2006). Adenomyosis exhibits a varied functional response to ovarian hormones. Proliferative glands and stroma generally are observed in the first half of the menstrual cycle. Adenomyosis may not respond to physiologic levels of progesterone, and secretory changes frequently are absent or incomplete during the second half of the cycle.

Variants of adenomyosis can suggest a malignant tumor. In one of these, endometrial tissue protrudes into myometrial vessels, simulating vascular invasion by a neoplasm, such as an endometrial stromal sarcoma (Fig. 72a). Intravascular endometrial tissue, consisting of endometrial stroma and glands or endometrial stroma alone, can be found in 5–12% of uteri with adenomyosis (Meenakshi and McCluggage 2010; Sahin et al. 1989). Intravascular adenomyosis usually appears to originate in the perivascular region and push into the vessel lumen; immunostains reveal the intravascular adenomyosis to be covered by a layer of CD31-positive endothelial cells (Fig. 72b). Cases of IVL may also contain endometrial glands and stroma and have been designated "intravascular adenomyomatosis" (Hirschowitz et al. 2013). Other problematic variants of adenomyosis include those where either the glandular or stromal component is altered or sparse. A low power clue that these represent adenomyosis is the circumferential muscular hypertrophy that surrounds foci of adenomyosis and the maintenance of a lobular appearance without surrounding stromal desmoplasia. In the gland-poor variant that tends to occur in elderly women, sometimes designated "adenomyosis with sparse glands," glands are few in number and some adenomyotic foci consist mainly or exclusively of endometrial stromal cells (Goldblum et al. 1995). Careful evaluation reveals that these variants of adenomyosis lack features of malignancy such as mitotic figures in the stromal cells and invasion into the surrounding myometrium and that they are almost always

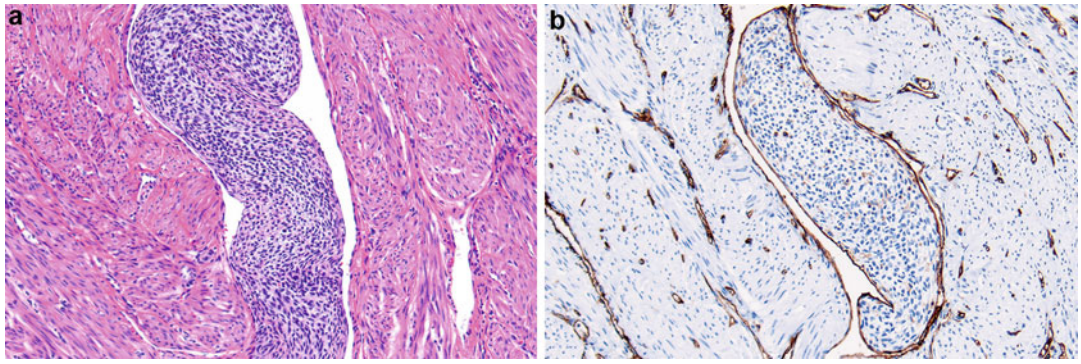

Fig. 72 Intravascular endometrial tissue in a patient with adenomyosis. (**a**) In this example no glands are present, raising the possibility of endometrial stromal sarcoma. However, there was no mass and no myoinvasive stromal tumor was present. Typical foci of adenomyosis were widely present in the region. (**b**) An immunostain for CD31 reveals that the vein is lined by a layer of endothelial cells. The intravascular endometrial tissue is completely covered by a layer of CD31-positive endothelial cells, suggesting that it is extravascular and has protruded into the vein lumen, pushing the endothelium over it

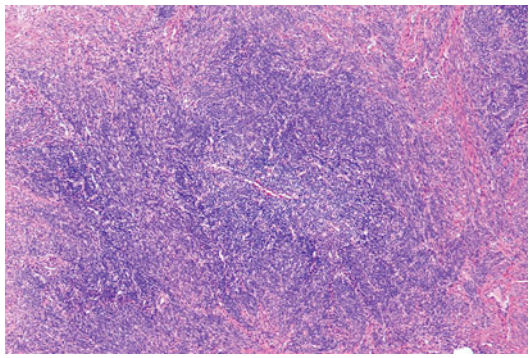

Fig. 73 Adenomyosis with sparse glands. Nearby foci of adenomyosis contained both glands and stroma, but this one consists of stroma only. The center is less cellular and appears pale. The periphery is more cellular and therefore is more darkly stained

accompanied by foci of typical adenomyosis. The gland-poor variant can be suspected at low power examination, as the stroma is frequently less cellular centrally than at the periphery, resulting in a focus of adenomyosis with a pale center and a darkly stained peripheral zone (Fig. 73). The stromal component can also be less conspicuous than usual and undergo modifications that make it difficult to recognize. It can be atrophic and fibrotic and may resemble the stroma of an atrophic endometrial polyp, with an eosinophilic, fibrillary appearance and loss of the monotonous, blue ovoid cells more typically associated with endometrial stroma. The eosinophilic, fibrillary appearance may superficially resemble myometrium, but high-power examination can reveal a clear demarcation between the surrounding, hypertrophic, well-organized bundles of myometrium and the disorganized, thin fibrils of altered endometrial stroma.

Most examples of adenomyosis contain endometrial stroma with a CD10-positive immunophenotype. The eosinophilic, fibrillary stroma found in atrophic adenomyosis frequently expresses CD10 only weakly or focally, so absent CD10 staining does not entirely exclude the presence of endometrial stroma and adenomyosis.

An adenomyoma is a circumscribed mass composed of smooth muscle, endometrial glands, and endometrial stroma (Gilks et al. 2000; Tahlan et al. 2006). The average patient age is 40–49, and the most common presentation is with abnormal bleeding. Leiomyomas may also be present in the uterus.

Grossly, an adenomyoma may be a rounded, sometimes cystic, tan mass within the myometrium, or it may involve or originate in the endometrium and grow as a polyp. About 2% of endometrial polyps are adenomyomas. Microscopically, endometrial glands and endometrial stroma are present within the mass, which typically consists mainly of smooth muscle. The

smooth muscle component of an adenomyoma generally consists of typical spindle-shaped smooth muscle cells, but epithelioid smooth muscle differentiation also occasionally occurs (Kenny and McCluggage 2014).

Adenomyomas also occur in the cervix, where they are more likely to be asymptomatic (Casey and McCluggage 2015; Gilks et al. 1996). They can grow as polyps that sometimes prolapse through the external os or as mural nodules. Cervical adenomyomas are composed of smooth muscle usually admixed with glands lined by columnar mucinous endocervical-type epithelium. The glands not infrequently have at least a focal lobular arrangement. Some also contain a component of tubal-type epithelium or endometrial-type glands and stroma. The admixture of endocervical-type glands and smooth muscle can raise the possibility of a minimal deviation adenocarcinoma ("adenoma malignum"). Unlike minimal deviation adenocarcinoma, a cervical adenomyoma is circumscribed or polypoid, does not infiltrate surrounding tissues, and does not display atypia, mitotic activity, or stromal reaction. Immunohistochemical stains for ER are generally positive in the glandular cells of an adenomyoma, while ER is generally negative in minimal deviation adenocarcinoma.

A rare variant of an adenomyomatous polyp, the APA, has atypical hyperplastic glands that usually contain foci of squamous metaplasia (Longacre et al. 1996; Heatley 2006). APA is discussed in detail in the chapter on benign endometrial conditions (▶ Chap. 7, "Benign Diseases of the Endometrium").

Various types of malignant neoplasms, such as variants of endometrial adenocarcinoma (Abushahin et al. 2011; Koike et al. 2013; Koshiyama et al. 2002) and adenosarcoma (Elshafie et al. 2013), have been reported to rarely arise in adenomyosis or in an adenomyoma.

Adenofibroma

First described in the cervix (Abell 1971), adenofibroma is a benign neoplasm that more typically occurs in the endometrium (Zaloudek and Norris 1981). It is composed of an admixture of histologically benign epithelial and mesenchymal elements.

Clinical Features and Gross Findings

Women with adenofibromas tend to be elderly. The median age is 68 years, and most patients are peri- or postmenopausal. Despite a predilection for the elderly, adenofibroma occurs in women of all ages, from less than 20 years to more than 80 years. There is no known association with race, nor does adenofibroma have the epidemiologic features of endometrial carcinoma. Abnormal vaginal bleeding is the most frequent complaint. Less common findings include abdominal pain, abdominal enlargement, or a polypoid tumor projecting from the cervix. Some patients have a history of prior removal of polyps.

Adenofibroma is a lobulated polypoid tumor that can arise anywhere in the uterus or in the cervix. It varies from soft to firm and is tan or brown. About 50% of adenofibromas contain small cysts that give the cut surface a spongy or mucoid appearance. The tumor ranges from 2 to 20 cm in maximum diameter, with a median of 7 cm. A large adenofibroma may fill the endometrial cavity and enlarge the uterus.

Microscopic Findings

Adenofibroma is composed of a mixture of histologically bland epithelium and mesenchyme that originates in the endometrium or cervix. Broad

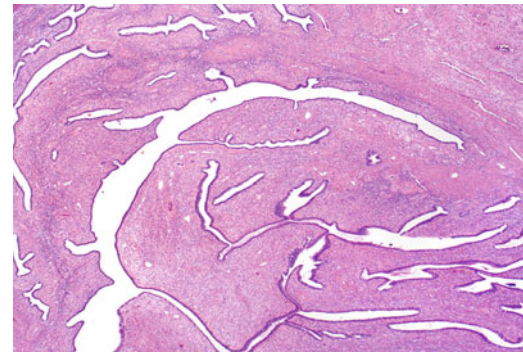

Fig. 74 Adenofibroma. Cleft-like glands and polypoid stromal projections are lined by benign epithelium in adenofibroma

papillary or polypoid fronds covered by epithelium project from the surface of the neoplasm and extend into cystic spaces within it (Fig. 74). Columnar or cuboidal epithelial cells, most often of endometrioid type, line cysts and cleft-like spaces. A mixture of various types of epithelia, including endocervical, tubal, and squamous, often occurs within the same neoplasm. The epithelium can be hyperplastic and stratified, but in this case the possibility that the tumor might be an APA should be carefully considered. Endometrioid and serous carcinoma have both been reported to involve adenofibromas; in such cases, the behavior is determined by the carcinoma and the patient should be treated accordingly (Miller and McClure 1992; Venkatraman et al. 2003).

The mesenchymal component is usually fibrous, consisting of fibroblasts and collagen (Fig. 75), but mixtures of endometrial stromal cells and fibroblasts are present in some neoplasms. The cellularity of the stroma is generally low and there is no periglandular condensation of stromal cells. The mesenchymal cells exhibit no nuclear atypia or mitotic activity. Rarely, histologically benign heterologous elements such as fat or skeletal muscle are present (Akbulut et al. 2008; Horie et al. 1995; Sinkre et al. 2000b). Adenofibromas are usually confined to the endometrium or cervical mucosa and do not invade the underlying myometrium or cervical stroma (Fig. 76). Two unique tumors that were classified as adenofibromas invaded the myometrium, and, in one case, myometrial veins (Clement and Scully 1990a). These tumors might well be viewed as adenosarcomas using current diagnostic criteria, since the stroma was moderately cellular and some mitotic activity was present in it; in general, any tumor classified as adenosarcoma for practical purposes is more likely to be an adenosarcoma than an adenofibroma.

Differential Diagnosis

Adenofibromas and benign endometrial or endocervical polyps can be difficult to distinguish. A papillary configuration or a vaguely "phyllodes-like" pattern in which polypoid stromal cores covered by benign epithelium project from the surface or into cystically dilated glands favors an adenofibroma. The stromal component of an adenofibroma tends to be more fibrous and more uniform than the stroma of a typical polyp.

The most important differential diagnosis is with adenosarcoma because adenofibroma and adenosarcoma have a somewhat similar appearance at low magnification. In the past this

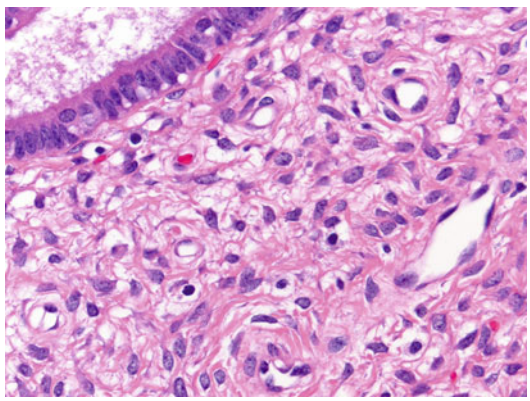

Fig. 75 Adenofibroma. The epithelium in an adenofibroma is benign, and in this example it is of endometrioid type. The stromal cells are benign and have pale oval or fusiform nuclei and ill-defined cell borders. No mitotic figures, hypercellular stroma, atypia or mitotic figures are present

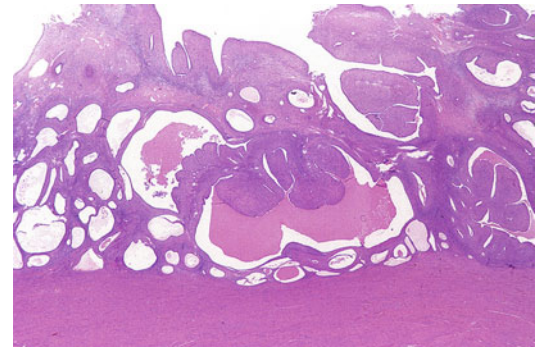

Fig. 76 Adenofibroma. A typical superficial tumor that is limited to the endometrium and does not invade the myometrium. No mitotic figures, hypercellular stroma, atypia or mitotic figures are present

differential diagnosis rested on finding hypercellular or atypical stroma with more than 4 MF/10 HPF in an adenosarcoma (Kaku et al. 1992; Zaloudek and Norris 1981). Over time the diagnostic criteria for adenosarcoma have been broadened to the point that some authors now doubt the existence of adenofibromas (Gallardo and Prat 2009) or at least doubt that they can be diagnosed in any type of specimen other than a hysterectomy (McCluggage 2016). We think that adenofibroma can be diagnosed, but only upon examination of the entire tumor to rule out the presence of abnormal areas indicative of adenosarcoma; this usually requires a hysterectomy. Features that are indicative of adenosarcoma include hypercellular periglandular stroma, stromal cell atypia, and virtually any detectable mitotic activity (Kurman et al. 2014). A practical approach is to classify any tumor with the appropriate architecture, a cellular or atypical stroma, and more than a rare mitotic figure as an adenosarcoma. Occasionally, a problematic adenofibromatous tumor occurs in a young woman where conservation of fertility is an important consideration. Such tumors can be designated as "atypical adenofibromatous tumors," but the pathology report should contain a note cautioning that a recurrence could have fully developed features of an adenosarcoma.

Clinical Behavior and Treatment

Hysterectomy is the preferred treatment for an adenofibroma because the neoplasm may recur if it is incompletely curetted or excised. Hysterectomy ensures complete removal and also permits the thorough sampling needed to exclude an adenosarcoma. Conservative therapy, such as hysteroscopy with repeat curettage or targeted resection, can be considered in situations in which hysterectomy is not the first choice of treatment, such as in a young woman who wishes to preserve her fertility. Adenofibroma is benign and no tumor-related deaths have been reported. Importantly, the clinical behavior of tumors with unusual gross or microscopic features is unclear and pathologists should be cautious about diagnosing such tumors as adenofibromas.

Adenosarcoma

Initially reported by Clement and Scully (1974), adenosarcoma is a biphasic tumor with benign epithelial elements and a sarcomatous stroma (McCluggage 2010). It comprises 5–6% of uterine sarcomas (Abeler et al. 2009) and most often occurs in the endometrium, although it can also arise in the cervix (Jones and Lefkowitz 1995) and in extrauterine pelvic locations such as the fallopian tube, ovary, and paraovarian tissues. Rarely, synchronous tumors occur in the uterus and an extrauterine site, such as the ovary.

Clinical Features

Adenosarcoma occurs in women of all ages. The median age is 50–59 years, with a range of 15–90 years. Extrauterine adenosarcoma occurs in younger women and is more aggressive than its uterine counterpart.

Adenosarcoma is not associated with obesity or hypertension. A few patients have a history of prior pelvic radiation, and occasional patients are diabetic. A few cases of adenosarcoma have been reported in women who have been treated for breast cancer with tamoxifen. Some patients have recurrent cervical or endometrial polyps and give a history of one or more prior polypectomies.

The most common presenting symptom is abnormal vaginal bleeding. Vaginal discharge, pain, nonspecific urinary symptoms, a palpable pelvic mass, and a tumor protruding from the

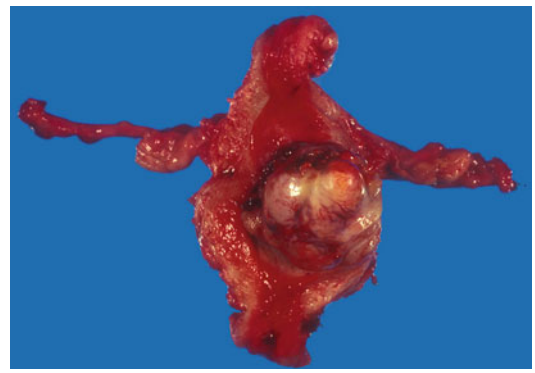

Fig. 77 Adenosarcoma. A polypoid tumor arises in the endometrium and fills the endometrial cavity

cervix are other common signs and symptoms. Most patients have stage I tumors at the time of diagnosis.

Gross Findings

Adenosarcoma most often arises in the endometrium and fills the uterine cavity, often resulting in an enlarged uterus. Rare tumors grow as nodules in the myometrium, presumably arising in adenomyosis. Adenosarcoma arises in the cervix in 5–10% of cases. Adenosarcoma is usually polypoid and averages 5–6 cm in maximum dimension (Fig. 77), although it occasionally grows as multiple papillary or polypoid masses. It can be either soft or firm. The cut surface is tan, brown, or gray, and zones of hemorrhage and necrosis are observed in about 25% of adenosarcomas. Small cysts are present in most tumors.

Microscopic Findings

Tubular glands and cleft-like spaces are distributed throughout the tumor, and papillary stromal fronds covered by epithelium project from the surface and into cysts (Fig. 78), resulting in a phyllodes tumor-like appearance (Clement and Scully 1990b; Zaloudek and Norris 1981). Glands are often present along with stroma in areas of myometrial invasion, which are observed in 15–52% of adenosarcomas. The surface and glandular epithelium most often resembles inactive or proliferative endometrial epithelium. Many other types of epithelium also occur in adenosarcomas, including secretory, mucinous, squamous, and clear cell. The epithelium typically is cytologically bland, but hyperplastic and even atypical hyperplastic epithelium is occasionally noted. Small foci of low-grade endometrioid adenocarcinoma can rarely be present in an adenosarcoma, and endometrioid adenocarcinoma also occasionally occurs in the endometrium adjacent to the adenosarcoma (Clement and Scully 1990b). If the adenocarcinoma is serous carcinoma or some other high-grade type of carcinoma, the tumor is best diagnosed as carcinosarcoma rather than adenosarcoma.

The mesenchymal component of an adenosarcoma is generally a low-grade homologous sarcoma such as low-grade endometrial stromal sarcoma or a fibroblastic/myofibroblastic

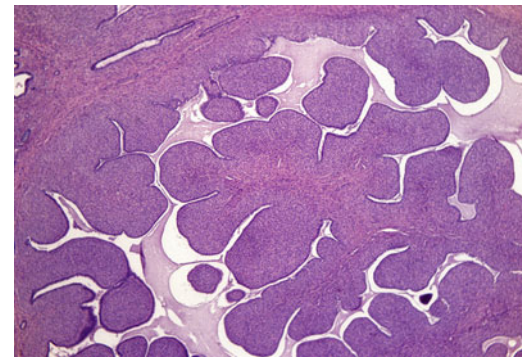

Fig. 78 Adenosarcoma. Papillary stromal fronds are lined by benign epithelium. The stroma is hypercellular, and the cellularity is greatest beneath the epithelium

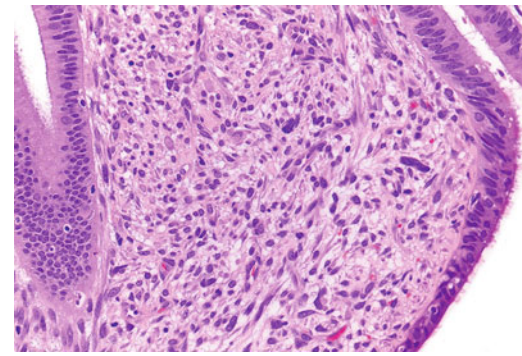

Fig. 79 Adenosarcoma. The stroma of an adenosarcoma is more cellular than that of an adenofibroma, especially in the vicinity of the epithelial component. The stromal cells usually resemble endometrial stromal cells or fibroblasts. The nuclei can be relatively uniform but, as in this case, atypia and pleomorphism can be conspicuous

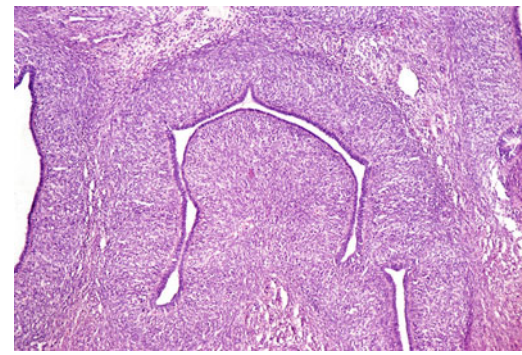

Fig. 80 Adenosarcoma. Periglandular stromal hypercellularity is a characteristic of adenosarcoma

sarcoma resembling the fibroblastic variant of low-grade endometrial stromal sarcoma (Fig. 79) (Clement and Scully 1990b; Gallardo and Prat 2009; Soslow et al. 2008). Smooth muscle is present in some tumors and can be conspicuous. Stromal hypercellularity is a characteristic feature of adenosarcoma and hypercellular stromal cuffs around glands (Fig. 80) or band-like hypercellular zones beneath the surface are present at least focally in almost every case. The degree of mesenchymal cell nuclear atypia is variable but is mild to moderate in most tumors. Mitotic figures are readily identified in most tumors and generally number $\geq$ 2–4/10 HPF. Mitotic figures tend to be most numerous in the cellular stromal cuffs around the glands. Neoplasms with the morphologic features of adenosarcoma (cellular stroma, periglandular cuffing, stromal cell atypia, and, in some cases, myometrial invasion), but in which mitotic activity is inconspicuous, can recur or metastasize. Therefore, a neoplasm with the typical appearance of an adenosarcoma in which atypical, hypercellular stroma is condensed around the epithelial elements should be diagnosed as an adenosarcoma even if there are only 1–2 MF/10 HPF. Adenosarcomas often contain bland areas indistinguishable from an adenofibroma, so extensive microscopic study may be required to identify a sarcomatous component.

Trabecular, insular, or tubular arrangements of plump epithelial-like cells, some having abundant foamy cytoplasm, are present in about 5% of adenosarcomas (Fig. 81) (Clement and Scully 1989; Gallardo and Prat 2009; Hirschfield et al. 1986). These structures, which are designated as sex cord-like elements, resemble the sex cord-like structures commonly seen in endometrial stromal tumors. Occasionally, overgrowth of the sex cord-like elements dominates the histologic picture. Tumors with overgrowth of sex cord-like elements appear to have the same prognosis as typical adenosarcomas, and this histologic pattern should not be viewed as a high-grade sarcomatous pattern or as sarcomatous stromal overgrowth (Stolnicu et al. 2016).

The mesenchymal component of an adenosarcoma is the significant component of the tumor in terms of histogenesis (Piscuoglio et al. 2016) and prognosis. Features of the mesenchymal component that may have prognostic significance and should be noted in the pathology report include its grade and mitotic activity, and the presence or absence of myometrial invasion, heterologous mesenchymal elements, and sarcomatous overgrowth.

In general, a high-grade sarcomatous component means that the tumor cells are markedly atypical, similar to those in pure high-grade sarcomas of the uterus and soft tissue. The nuclei in such tumors have been characterized as showing 3 + atypia on a scale of 0–3+ (Clement and Scully 1990b; Zaloudek and Norris 1981), or as showing nuclear atypia and pleomorphism identifiable at

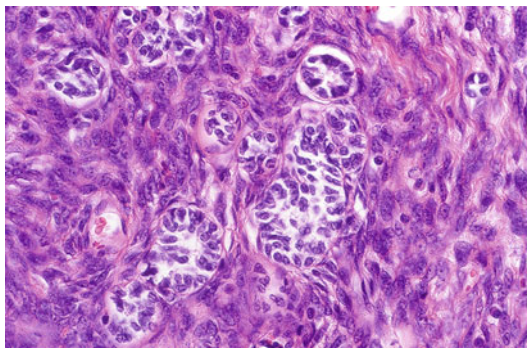

Fig. 81 Adenosarcoma. Sex cord-like trabeculae or tubules are occasionally present in the stroma of an adenosarcoma

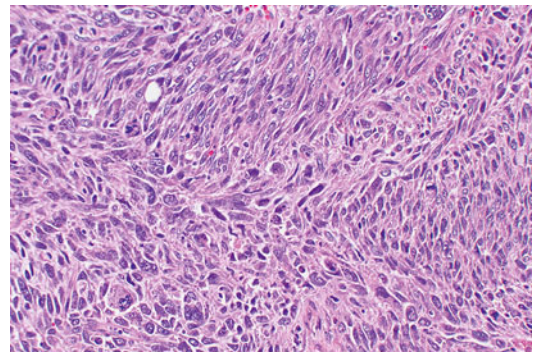

Fig. 82 Adenosarcoma with sarcomatous overgrowth. A high-grade spindle cell sarcoma has developed in an adenosarcoma and comprises more than 25% of the tumor volume

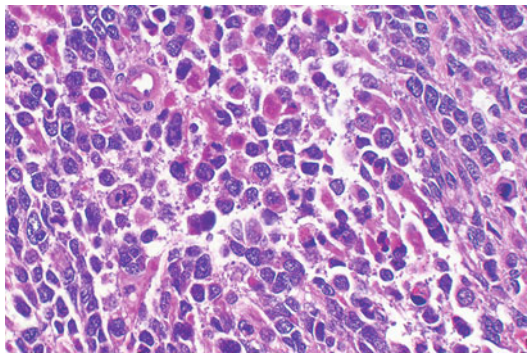

Fig. 83 Adenosarcoma with rhabdomyosarcoma in zones of sarcomatous overgrowth. Rhabdomyoblasts are round or spindle-shaped and have prominent eosinophilic cytoplasm. It is sometimes possible to identify cross striations, but these days immunohistochemistry is typically used to confirm the presence of rhabdomyoblasts

low magnification (Gallardo and Prat 2009; Hodgson et al. 2017).

Sarcomatous overgrowth, reported to be present in 33–50% of cases, is said to occur when the sarcomatous component of the tumor occupies 25% or more of the total tumor volume (Bernard et al. 2013; Carroll et al. 2014; Gallardo and Prat 2009; Kaku et al. 1992). In these areas, epithelial elements are absent, and the mesenchymal component is typically of high grade, with increased cellularity and mitotic activity and greater nuclear atypia (Fig. 82) compared with the background adenosarcoma, although occasionally the grade is the same as that of the background (Clement 1989). The sarcoma can be stromal sarcoma, fibrosarcoma, or leiomyosarcoma, or a mixture of elements. Heterologous elements, particularly rhabdomyosarcoma (Fig. 83), may occur in and be limited to the zone of sarcomatous overgrowth. The zones of pure sarcomatous growth can be present in or constitute the entire myoinvasive component of an adenosarcoma. Lymphovascular invasion, which is rare in adenosarcoma, is most often found in zones of sarcomatous overgrowth.

Heterologous mesenchymal elements are present in 20–25% of adenosarcomas. Striated muscle, which typically resembles embryonal rhabdomyosarcoma, is the most common heterologous element, but cartilage, fat, and other elements are occasionally observed. Rhabdomyosarcoma is characterized by the presence of round-to-spindled tumor cells with atypical hyperchromatic nuclei and variable amounts of eosinophilic cytoplasm. Cytoplasmic cross striations can occasionally be identified in rhabdomyoblasts on H&E-stained slides, but immunohistochemical staining for desmin and myogenin is now more widely used to identify rhabdomyoblastic differentiation. Rhabdomyosarcoma can be present in adenosarcomas with and without sarcomatous overgrowth, although it is more commonly present in tumors with overgrowth. In one study, the presence of rhabdomyosarcoma was associated with myoinvasion and lower overall survival (Mentrikoski et al. 2015).

Immunohistochemistry and Molecular Pathology

The epithelial component of adenosarcoma is keratin-positive and usually stains for ER and PR. The mesenchymal component often resembles endometrial stromal sarcoma, so it is not surprising that adenosarcoma and endometrial stromal sarcoma share many immunophenotypic features. The mesenchymal cells in adenosarcoma typically show cytoplasmic staining for CD10 and nuclear staining for ER and PR and for WT-1 (Amant et al. 2004; Soslow et al. 2008). Staining is often most conspicuous in the periglandular stromal cuffs where the cell density is greatest. Staining for CD10 and hormone receptors is often weaker or lost in areas of high-grade sarcomatous overgrowth. Increased levels of nuclear staining for the proliferation marker Ki-67 (MIB-1) are typically present in hypercellular periglandular zones and in areas of sarcomatous stromal overgrowth (Gallardo and Prat 2009). Distinctive periglandular cuffs of Ki-67-positive mesenchymal cells can be helpful in the diagnosis of adenocarcinoma; these are not seen in some entities in the differential diagnosis such as endometrial polyps and APA (Aggarwal et al. 2012). Aberrant staining (diffuse strong positive staining in >80% of tumor cell nuclei or complete loss of staining) for p53 is sometimes noted particularly in cases of

high-grade adenosarcoma which are most likely to have *p53* mutations (Hodgson et al. 2017). Focal staining for keratin, sometimes with a dot-like pattern, is occasionally noted in the mesenchymal component, and patchy weak staining for smooth muscle actin and/or desmin is present in many adenosarcomas. Areas of smooth muscle and rhabdomyosarcomatous differentiation show strong positive cytoplasmic staining for desmin, and rhabdomyosarcoma shows positive nuclear staining for myogenin.

A number of cytogenetic and molecular studies on adenosarcoma have been reported in recent years. In general, these have found alterations in adenosarcomas, but abnormalities have only been identified in around half or fewer of the cases studied. In one study, cytogenetic abnormalities were identified in 45% of adenosarcomas. Aneuploidy with many translocations was observed in two cases, and less complex abnormalities were found in seven, including chromosome 8 alterations such as rearrangements of 8q13 or extra copies of chromosome 8 (Howitt et al. 2016). Molecular studies have revealed occasional mutations in genes such as *ATRX*, *FGFR2*, *KMT2C*, and *DICER1*. Some studies have found *TP53* mutations to be infrequent (Howitt et al. 2015b), but one focused on high-grade adenosarcomas found them to be frequent and accompanied by aberrant immunohistochemical staining (Hodgson et al. 2017). In general, copy number variations have been more prominent than specific mutations and have included amplifications of *MDM2*, *CDK4*, *HMGA2*, and *TERT*, among others (Hodgson et al. 2017; Howitt et al. 2015b; Lee et al. 2016; Piscuoglio et al. 2016).

Differential Diagnosis

The differential diagnosis includes benign entities such as endometrial and endocervical polyps and adenofibroma, as well as various malignant tumors, including endometrial stromal sarcomas, other uterine sarcomas, and, in young patients with cervical tumors, botryoid rhabdomyosarcoma.

Many patients with adenosarcoma have a history of prior removal of "polyps." In general, polyps are smaller than adenosarcomas. Microscopically, the stroma of benign polyps tends to be fibrous, with few if any mitotic figures. Polyps often have conspicuous central blood vessels. Problems arise when large polyps have more cellular zones with endometrial-type stroma, where mitotic activity can overlap with the lower end of the range seen in adenosarcoma (Hattab et al. 1999). However, polyps lack the characteristic architecture of an adenosarcoma, do not have periglandular stromal hypercellularity, usually lack nuclear atypia, and do not display mitotic activity at the level commonly present in adenosarcoma (>4 MF/10 HPF). Rare atypical polyps exhibit some features of an adenosarcoma, such as abnormal architecture, increased periglandular cellularity, or increased mitotic activity, in the stromal cells, but in polyps the features are focal or incompletely developed, the polyps are small (<3 cm), and do not exhibit the clinical behavior of an adenosarcoma (Howitt et al. 2015a). Bizarre stromal cells are occasionally present in polyps, but these appear to represent a degenerative phenomenon, since the cells have smudged nuclear chromatin and are not mitotically active (Tai and Tavassoli 2002).

Adenofibroma is a rare benign tumor of the cervix or endometrium. The overall architecture is similar to adenosarcoma, but the stroma is predominantly fibrous and less cellular than that of an adenosarcoma, with no condensation of stromal cells around the epithelial elements. The stromal cells are bland, and mitotic figures are absent or difficult to find. Some adenosarcomas contain bland areas similar in appearance to an adenofibroma, so the diagnosis of an adenofibroma generally requires hysterectomy so that the entire tumor can be evaluated microscopically (McCluggage 2016). Several authors have noted that it is occasionally difficult to differentiate between an adenofibroma and a low-grade adenosarcoma (Clement and Scully 1990b; Gallardo and Prat 2009).

The stroma of an adenosarcoma often resembles endometrial stromal sarcoma or one of its variants, so distinguishing the two may require careful examination. Endometrial stromal sarcoma can incorporate benign glands at its periphery, but glands tend to be absent away from the edges of the tumor, while in adenosarcoma

glands are distributed throughout. Stromal sarcoma often contains epithelial or sex cord-like elements, but these do not resemble the epithelium present in adenosarcoma. Rare stromal sarcomas contain endometrial-type glands, which are often irregularly distributed in the tumor such that many areas lack glands. Also, the stroma does not condense around the glands, and the phyllodes-like architecture of an adenosarcoma is not seen.

Other pure sarcomas of the uterus or cervix can incorporate benign glands at their periphery. However, no glands are present in most parts of the tumor and the sarcoma tends to be of significantly higher grade than the mesenchymal element of an adenosarcoma. A high-grade mesenchymal component is present in an adenosarcoma with stromal overgrowth, but such tumors almost always have areas with the typical architecture and low-grade mesenchymal elements that characterize an adenosarcoma, and these can be identified if the tumor is adequately sampled.

In a young patient, a botryoid rhabdomyosarcoma of the cervix enters the differential diagnosis. Botryoid rhabdomyosarcomas have a polypoid surface contour similar to that seen in adenosarcoma, and the hypercellular subsurface zone commonly referred to as the "cambium layer" resembles the stromal hypercellularity seen around epithelial elements in an adenosarcoma (Daya and Scully 1988; Ferguson et al. 2007). However, glands are usually not distributed throughout a rhabdomyosarcoma, and the mesenchymal cells, some of which are usually recognizable as rhabdomyoblasts, tend to be more primitive and mitotically active than the stromal cells of an adenosarcoma. Immature cartilage is present in many cervical rhabdomyosarcomas.

Carcinosarcoma, like adenosarcoma, has both epithelial and mesenchymal components. However, in carcinosarcoma the epithelial component is an adenocarcinoma or an undifferentiated carcinoma and the mesenchymal component is a sarcoma, usually of high grade. In the rare cases in which focal low-grade endometrioid adenocarcinoma is encountered in an adenosarcoma, the diagnosis is the former. A low-grade adenocarcinoma associated with the type of low-grade sarcoma usually present in an adenosarcoma should not be mistaken for a carcinosarcoma, in which both components are typically of high grade.

Clinical Behavior and Treatment

Adenosarcoma is usually treated by hysterectomy and bilateral salpingo-oophorectomy, although a few young patients have been treated by local excision of the tumor. Metastasis to lymph nodes is rare, although occasional patients whose tumors show sarcomatous overgrowth have pelvic lymph node metastases (Machida et al. 2017). Adenosarcoma is not as aggressive as carcinosarcoma, but it recurs in 25–40% of patients and occasionally follows an aggressive course. Recurrence is generally in the pelvis or vagina, but distant metastases occur in 5% of patients (Clement and Scully 1990b). Recurrences typically consist exclusively of the sarcomatous component, but both epithelium and stroma are occasionally present. Pathologic features of the primary tumor that are associated with an increased risk of recurrence or metastasis are extrauterine spread at diagnosis; myometrial invasion, especially into the outer half of the myometrium; lymphovascular space invasion; and sarcomatous overgrowth of the mesenchymal component. Prognosis does not clearly correlate with mitotic rate in the mesenchymal component. Other features that have been proposed as poor prognostic findings include high tumor grade (Hodgson et al. 2017) and the presence of heterologous rhabdomyoblastic differentiation (Mentrikoski et al. 2015), but it is difficult to evaluate the independent contribution of these features to the prognosis because they tend to co-vary with sarcomatous overgrowth. Patients with adenosarcoma with sarcomatous overgrowth of the mesenchymal component have been reported to have a prognosis similar to that of women with carcinosarcoma (Krivak et al. 2001), but recent studies have shown that patients who have sarcomatous overgrowth have better outcomes if they receive adjuvant therapy (Bernard et al. 2013; Carroll et al. 2014; Tanner et al. 2013). Extended clinical observation is necessary because recurrence typically occurs long

(3.5–5 years) after treatment. About a quarter of patients with adenosarcoma die of tumor, often more than 5 years after initial diagnosis.

UTROSCT

The tumors in this category were initially described by Clement and Scully, who recognized two variants (Clement and Scully 1976). One variant, the type I tumors, has been shown to be an endometrial stromal nodule or sarcoma containing significant areas (>10% of the tumor) of epithelial-like structures that appear similar to an ovarian sex cord–stromal tumor. Tumors of this type are commonly referred to as endometrial stromal tumors with sex cord-like elements, or ESTSCLE, and are discussed in the section of this chapter that deals with endometrial stromal tumors. The second variant, the type II tumors, consists predominantly or exclusively of sex cord-like elements, and tumors of this type are referred to as UTROSCT. Tumors of the latter type are discussed in this section.

Clinical Features and Gross Findings

Uterine tumors with sex cord-like elements occur in middle-aged women; the average age is around 50 (Blake et al. 2014). The main symptom is abnormal bleeding or pelvic pain. Most patients have an enlarged uterus or a palpable uterine mass.

UTROSCTs are intramural or submucosal nodules surrounded by myometrium or polypoid tumors that grow into the endometrial cavity. They are yellow or tan and have a circumscribed or slightly irregular periphery. The average diameter is 6–7 cm.

Microscopic Findings

Microscopically, most are circumscribed, but examples with infiltrative margins and, rarely, vascular invasion have been reported. The tumor cells form plexiform cords, trabeculae, and nests, and may line well-formed tubules with lumens (Fig. 84). Glomeruloid formations or tubules with a retiform appearance are occasionally present. In some tumors, retiform tubules dominate the histologic picture; designation of these as retiform RUTROSCT has been proposed (Nogales et al. 2009).

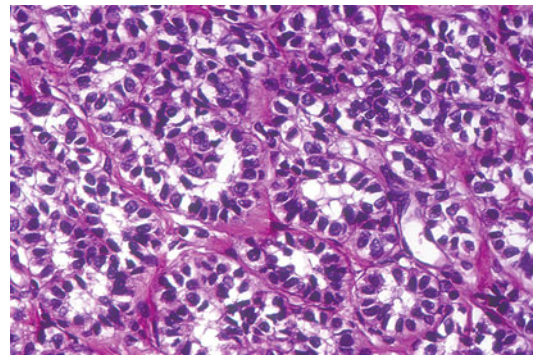

Fig. 84 UTROSCT. The low columnar tumor cells grow in a tubular pattern with scanty stroma

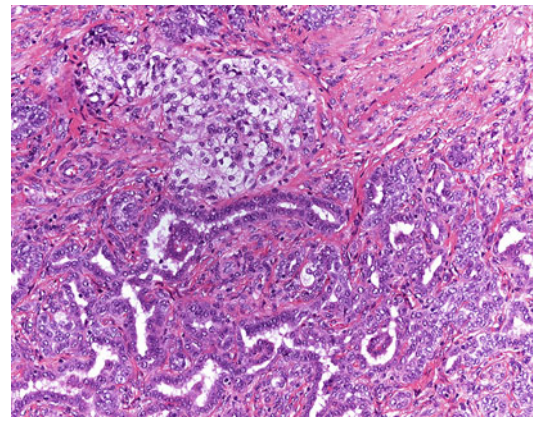

Fig. 85 UTROSCT. This tumor contains tubules lined by low columnar cells and nests of polygonal cells with abundant foamy cytoplasm

The tumor cells have uniform small bland nuclei with inconspicuous nucleoli, and mitotic figures are rare, with ≥2 MF/10 HPF regarded as "significant mitotic activity" (Moore and McCluggage 2017). The cytoplasm varies from scant to moderate and is typically eosinophilic, although occasional tumors contain cells with abundant pale foamy cytoplasm. The cells are spindled, cuboidal, or columnar in shape. Columnar sertoliform cells, polygonal cells with

eosinophilic or foamy cytoplasm (Fig. 85), or cells resembling granulosa cells are present in some tumors. The stroma ranges from endometrial-like to hyaline or fibrous and smooth muscle is present in some UTROSCT. Stroma accounts for less than 50% of the tumor and is often scanty. The histogenesis of UTROSCT is unclear; an origin from endometrial stroma or uncommitted cells in the uterus has been proposed.

Immunohistochemistry and Molecular Pathology

Diverse immunohistochemical results have been described in tumors of this type, but the sex cord-like structures are usually immunoreactive for vimentin; cytokeratin; sex cord markers including calretinin (Fig. 86), inhibin (Fig. 87), CD 99, Melan-A, CD56, and WT-1; and, often, smooth muscle actin or desmin (de Leval et al. 2010; Hurrell and McCluggage 2007; Irving et al. 2006). Variable staining has been reported for FOXL2, including strong nuclear staining in 1 of 15 tumors and weak or moderate staining in 5 additional tumors in one study (Chiang et al. 2015) and strong positive staining in 2 of 19 tumors as well as weak or moderate staining in 8 additional tumors in another (Croce et al. 2016). Importantly, however, endometrial stromal cells typically show weak to moderate nuclear staining for FOXL2. Steroidogenic factor-1 (SF-1) has also been shown to stain UTROSCT, being strongly positive in 1 of 19 tumors and showing weak or moderate staining in another 10, with no staining in endometrial stromal cells (Croce et al. 2016). Similar findings were reported in a smaller number of cases in another series, where it was noted that none of the tumors likely to mimic a UTROSCT showed staining for SF-1 (Stewart et al. 2016b). Immunostains for EMA have been reported as negative in most tumors, but weak to moderate staining was reported in one study of four cases (Hurrell and McCluggage 2007). Positive staining for ER and PR is often present. Positive staining for two or more markers of sex cord differentiation is seen in most UTROSCTs, with calretinin being the marker most likely to be positive (Irving et al. 2006; Pradhan and Mohanty 2013).

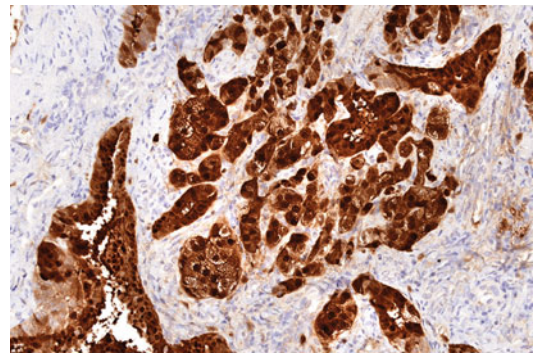

Fig. 86 UTROSCT. Sex cord-like tubules show strong positive staining for calretinin in this UTROSCT

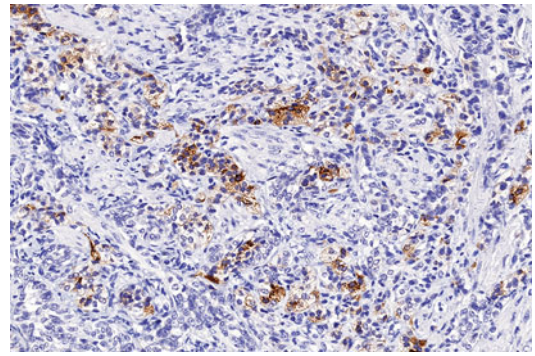

Fig. 87 UTROSCT. Cord-like arrangements of cells, many with foamy cytoplasm, show modest but definite staining for inhibin in this UTROSCT

Molecular studies indicate that these tumors do not harbor *JAZF1-SUZ12* gene fusions, nor do they show *PHF1* rearrangements, indicating that they are unlikely to be endometrial stromal neoplasms (Staats et al. 2009). Neither *FOXL2* nor *DICER1* mutations have been identified in any UTROSCT tested for these mutations, though some of the tested tumors showed limited immunohistochemical staining for FOXL2 (Chiang et al. 2015; Croce et al. 2016).

Differential Diagnosis

The differential diagnosis includes an ESTSCLE, adenosarcoma, endometrioid adenocarcinoma with

a sex cord-like pattern, epithelioid smooth muscle tumor, and, less likely, a carcinosarcoma. ESTSCLE almost invariably contain recognizable areas of typical endometrial stromal tumor, and they are more likely than a UTROSCT to invade the myometrium or grow into blood vessels. The endometrial stromal areas usually show strong positive staining for CD10, ESTSCLE tends to show less staining for sex cord-stromal markers than UTROSCT, and FISH or molecular testing may show rearrangements of *JAZF1* or *PHF1*, which are not present in UTROSCTs.

As discussed above, adenosarcoma is a biphasic neoplasm in which benign epithelium is admixed with malignant mesenchyme. Differentiating between a UTROSCT and an adenosarcoma is usually straightforward, but some adenosarcomas contain sex cord-like elements. Rarely, these sex cord-like elements are so extensive that they dominate the histologic appearance of the tumor (Stolnicu et al. 2016), and such a neoplasm could be difficult to differentiate from a UTROSCT. The location of the tumor helps with this differential diagnosis as adenosarcoma generally originates in the endometrium and grows into the endometrial cavity, while UTROSCT is typically located within the myometrium. Nevertheless, there is some overlap; to make the correct diagnosis, adequate sampling of the specimen is necessary to identify areas of the tumor that display the characteristic morphology of an adenosarcoma.

Endometrioid adenocarcinomas is a sex cord-like growth pattern almost always contain gland forming elements, would be negative for sex cord-associated markers and tend to express EMA, unlike UTROSCT.

Epithelioid smooth muscle tumors may have a corded and trabecular architecture that superficially resembles sex cords. In contrast to UTROSCT, these tumors tend to stain differently smooth muscle marker while they lack expansion of sex cord-associated markers.

Finally, a carcinosarcoma could potentially enter the differential diagnosis, but the immunophenotype together with the absence of high-grade carcinomatous and sarcomatous components differentiates these rare tumors from a carcinosarcoma.

Clinical Behavior and Treatment

The clinical behavior of these tumors is difficult to assess because in some studies a clear distinction has not been made between ESTSCLE and UTROSCT. Where the distinction has been made, UTROSCT have typically been reported to generally have a benign clinical evolution, although rare examples have exhibited more aggressive behavior, extending beyond the uterus or metastasizing. In a recent report of 34 cases, including 32 drawn from a pathology consultation practice, it was found that 8 patients (23.5%) developed metastases and 3 (8.8%) died (Moore and McCluggage 2017). Tumor necrosis and significant mitotic activity ($\geq$2 MF/10 HPF) were the main factors associated with an adverse outcome. UTROSCT appears to have more malignant potential than has been appreciated up to now. Nevertheless, the literature contains reports of cases in which conservative uterus sparing surgery was successfully used in a young woman to conserve fertility (Hillard et al. 2004).

IMT

IMT is an uncommon uterine spindle cell tumor that typically has a prominent myxoid stroma that contains variable numbers of chronic inflammatory cells. It was initially considered to be an inflammatory pseudotumor (Gilks et al. 1987), but the documentation of the clonal nature of some IMT and the demonstration of chromosomal rearrangements involving the *ALK* locus indicate that these are best viewed as neoplasms.

Clinical Features and Gross Findings

IMT occurs in all age groups, from children to postmenopausal women. The average patient age is around 40. The presentation is with abnormal bleeding or symptoms related to the presence of a mass, such as pain or pressure, but some patients have constitutional symptoms including fever, weight loss, and fatigue. Occasionally, the tumor is an incidental finding at cesarean section or at surgery performed for another condition.

Grossly, the tumors range up to 12 cm in maximum diameter. The average diameter is 5–7 cm. They are firm or soft, and the cut surfaces are tan or white and often described as mucoid or gelatinous.

Microscopic Findings

Microscopically, the myofibroblastic tumor cells are spindle shaped, stellate, or epithelioid and have pale eosinophilic cytoplasm (Fig. 88). Their nuclei are granular or vesicular, and they may have prominent nucleoli. Nuclear atypia is mild or moderate in most cases, but marked atypia is seen in some tumors. Mitotic activity is variable and mostly ranges from 2 to 5 MF/10 HPF. Occasional tumors exhibit greater mitotic activity, sometimes exceeding 10 MF/10 HPF. Atypical mitotic figures are generally not present. A lymphoplasmacytic infiltrate is invariably present in these tumors. It ranges from mild and visible only at higher magnification to marked and diffuse, visible at low magnification. Three basic histologic patterns have been described: a myxoid pattern with lymphocytes and plasma cells scattered among the tumor cells, a compact cellular pattern in which the spindle cells are arranged in fascicles mimicking a smooth muscle tumor, and a hyalinized or collagenous pattern (Rabban et al. 2005). Myxoid changes and inflammatory infiltrates can be present only focally. Mixtures of the three main patterns are common in individual tumors. An infiltrative tumor border is almost always present. Infiltrative growth can take the form of finger-like projections of tumor cells into the surrounding myometrium, an irregular zigzag or sawtooth tumor periphery, or clusters of cells or single cells that infiltrate the myometrium.

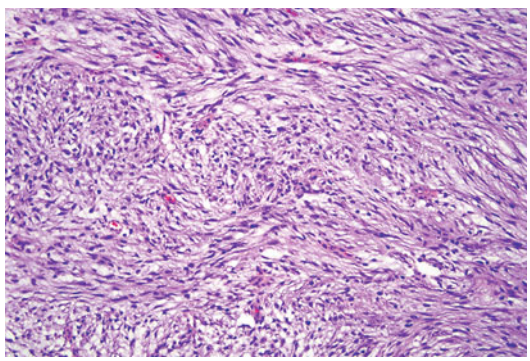

Fig. 88 IMT. The tumor is a histologically low-grade spindle cell proliferation of largely mitotically inactive spindle cells set in a myxoid and inflammatory background. (Courtesy of Joseph Rabban, M.D.)

Immunohistochemistry and Molecular Pathology

Immunohistochemical stains for smooth muscle actin, desmin, and, usually, CD10 show moderate or marked staining in the tumor cell cytoplasm. Caldesmon is less likely to stain. Immunostains for ER and PR are generally but not invariably positive. IMT shows cytoplasmic staining for ALK in 90% or more of cases (Bennett et al. 2017a; Fuehrer et al. 2012; Parra-Herran et al. 2015; Rabban et al. 2005). The staining is variable in intensity and distribution but is often strong and diffuse. *ALK* staining is usually coarsely granular, although it can also be homogeneous and can show membrane or perinuclear accentuation. A low threshold for performing *ALK* immunostains appears warranted to avoid misclassifying IMTs as smooth muscle tumors; any uterine tumor with any degree of myxoid changes or any lymphoplasmacytic infiltration should be considered for staining (Pickett et al. 2017).

FISH testing reveals *ALK* rearrangements in at least 70–80% of tumors (Parra-Herran et al. 2015), and various fusion partners have been detected by molecular analysis (Bennett et al. 2017a; Haimes et al. 2017). Fusion partners that have been detected include *THBS1*, *IGFBP5*, *DES*, *FN1*, *SEC31*, and *TIMP3*; *THBS1* and *IGFBP5* appear to be the most common fusion partners. *IGFBP5*, *DES*, and *FN1* are located on the same chromosome as *ALK* and are thought to arise via chromosomal inversions. FISH analysis consequently may not reveal *ALK* rearrangements when the fusion partner is one of these genes. A negative FISH result should therefore not exclude a diagnosis of IMT if the histologic appearance of the tumor suggests the diagnosis and immunohistochemistry for ALK is positive (Haimes et al. 2017). *ROS1* rearrangements have been documented in extrauterine IMT, but to date none have been reported in uterine IMT.

Differential Diagnosis

Cases of IMT have undoubtedly been misdiagnosed as other tumor types in the past. Tumors with which IMT is easily confused are smooth muscle tumors, including leiomyomas, leiomyosarcomas and STUMP (Pickett et al. 2017). Myxoid leiomyosarcoma is a particular problem, along with other myxoid mesenchymal tumors of the uterus such as myxoid variants of endometrial stromal sarcoma and, occasionally, solitary fibrous tumors (SFT) (Busca and Parra-Herran 2017).

Myxoid leiomyosarcoma is an uncommon variant of leiomyosarcoma that is characterized by abundant myxoid stroma that is present in at least 50% of the tumor. The degree of nuclear atypia and mitotic activity varies, but some myxoid leiomyosarcomas display less nuclear atypia and mitotic activity than a conventional leiomyosarcoma, and the malignant nature of the tumor is recognized by the combination of the myxoid nature of the tumor and invasive growth into the surrounding myometrium. The morphologic appearance of myxoid leiomyosarcoma overlaps with that of IMT; performing immunohistochemistry, and possibly FISH testing, for *ALK* rearrangement is essential to differentiate between these tumor types. Immunohistochemical staining for p53 and p16 may also be helpful, as mutations in *TP53* and *CDKN2A* occur in about 50% of myxoid leiomyosarcomas, and result in aberrant staining patterns for p53 and complete loss of staining for p16 (Schaefer et al. 2017). Diffuse strong staining for p16 in the absence of any mutation is also seen in some myxoid leiomyosarcomas. In contrast, abnormalities in p53 and p16 staining are uncommon in IMT. Thus, immunohistochemical staining for ALK, p53, and p16 can assist with the differential diagnosis between an IMT and a myxoid leiomyosarcoma. Benign myxoid leiomyomas are rare and pose less of a diagnostic problem; absence of staining for ALK provides support for a diagnosis of a myxoid leiomyoma rather than an IMT.

Both low- and high-grade variants of endometrial stromal sarcoma (ESS) can have myxoid features. Low-grade variants of endometrial stromal sarcoma have abundant myxoid stroma, but they show the same patterns of myometrial and vascular invasion that are seen in more typical examples of low-grade ESS, a similar capillary vascular pattern is seen, and the tumor cells resemble endometrial stromal cells or fibroblasts (Oliva et al. 1999). Positive staining for CD10 is typically present in ESS, but this is frequently observed in IMT as well, so staining for ALK is required to differentiate these two tumor types.

High-grade endometrial stromal sarcomas associated with *ZC3H7B-BCOR* gene fusions or ITD of *BCOR* also have a myxoid appearance and can mimic an IMT or myxoid leiomyosarcoma (Hoang et al. 2017; Lewis et al. 2018; Marino-Enriquez et al. 2018). These have permeative, tongue-like or pushing invasion of the myometrium, variable nuclear atypia, usually frequent mitotic figures, and variable amounts of myxoid stroma. They show positive staining for cyclin D1 and may show staining for CD10 and BCOR; they can be differentiated from an IMT by a lack of staining for ALK. Staining for BCOR does not appear to be a completely reliable way to identify these tumors, since many of them show weak, focal, or absent staining, and BCOR also stains high-grade endometrial stromal sarcomas with *YWHAE-NUTM2*, indicating that molecular testing is required to confirm the diagnosis of a BCOR-related endometrial stromal sarcoma.

Finally, SFT can have myxoid stroma and occasionally involve the uterus. SFT are cellular spindle cell tumors with a patternless arrangement and prominent blood vessels. They show positive nuclear staining for STAT6 and cytoplasmic staining for CD34. STAT 6 and CD34 tend to be negative in IMT, although in one study a single case of IMT showed positive staining (Yang et al. 2018). SFT is ALK negative, so the morphologic appearance and immunophenotype generally readily differentiate these two types of tumor.

Clinical Behavior and Treatment

Most IMTs are clinically benign, but a significant minority, 20–30%, show extrauterine spread at diagnosis or recur, usually within the pelvis or abdomen, and tumors with extrauterine spread can behave aggressively and cause the death of the patient. Features that are associated with aggressive behavior include older patient age, large tumor size, lymphovascular space invasion, tumor cell necrosis, and high mitotic activity, frequently in excess of 10 MF/10 HPF (Bennett et al. 2017a). The *ALK* rearrangements present in these tumors theoretically make them amenable to targeted therapy, and responses to crizotinib have been reported (Pickett et al. 2017; Subbiah et al. 2015).

Heterologous and Homologous Sarcomas Other than Leiomyosarcoma and Endometrial Stromal Sarcoma

The tumors in this category are high-grade sarcomas that often resemble the mesenchymal component of a carcinosarcoma. Most pleomorphic homologous sarcomas arise in the endometrium and consist of round or spindled cells with variable amounts of cytoplasm and pleomorphic atypical nuclei. These are a type of undifferentiated endometrial sarcoma and are discussed in the section on undifferentiated uterine sarcoma. Some may result from sarcomatous stromal overgrowth in an adenosarcoma or carcinosarcoma or by dedifferentiation of a low-grade endometrial stromal sarcoma. Although most undifferentiated sarcomas are of endometrial origin, a few appear to arise in the myometrium, either from nonspecific mesenchymal elements or by dedifferentiation of a leiomyosarcoma fibromatous sarcoma has recently been described with *NTRK* fusions (Chiang et al. 2018).

Pure heterologous sarcomas occasionally arise in the uterus. Some are assumed to represent complete heterologous stromal overgrowth in an adenosarcoma or carcinosarcoma. Rhabdomyosarcoma and angiosarcoma are the most common heterologous uterine sarcomas, but chondrosarcoma, osteosarcoma, liposarcoma, and tumors containing mixtures of heterologous elements also occur (Fadare 2011). Histologically benign heterotopic bone, cartilage, and fat are occasionally found in the uterus, and rare benign tumors contain one or more of these elements (Roth and Taylor 1966). They should not be mistaken for heterologous sarcomas or carcinosarcomas, in which the mesenchymal elements are histologically malignant.

Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant neoplasm that displays skeletal muscle differentiation. It is the most common soft tissue tumor in children and approximately 20% of pediatric rhabdomyosarcoma originate in the genital tract. In adults, rhabdomyosarcoma of the female genital tract is a rare tumor that can involve either the cervix or the body of the uterus.

Rhabdomyosarcoma of the uterus and cervix is categorized into three major variants with significant differences in clinical behavior and prognosis. The most common and generally most favorable variant is embryonal rhabdomyosarcoma, which includes botryoid and anaplastic histologic subtypes. The other two types of rhabdomyosarcoma, alveolar and pleomorphic rhabdomyosarcomas, are less common and usually have a significantly less favorable clinical outcome.

Clinical Features

In adults, rhabdomyosarcomas can occur at any age, including young to middle-aged women with predominantly cervical tumors and older women in the fifth to seventh decade, mainly with tumors of the uterine corpus. The most common presenting symptom is abnormal vaginal bleeding. The majority of women, approximately 75%, present with local or regional disease. The primary site is the cervix in approximately one-half of women, making it the most common site of origin of genital tract rhabdomyosarcoma in adults; only 20% of tumors are uterine.

Children and young adults with cervical or uterine rhabdomyosarcomas present with vaginal bleeding or with a polypoid tumor that protrudes from the vagina. Children with cervical rhabdomyosarcoma have an average age of 12 years (Dehner et al. 2012), but identical tumors occur in young and middle-aged women (Daya and Scully 1988; Li et al. 2013). Cervical rhabdomyosarcoma occurs in patients with the DICER1 syndrome in up to 20% of cases (Stewart et al. 2016a). Other tumors that occur in patients with the syndrome include pleuropulmonary blastoma, cystic nephroma, multinodular goiter, and Sertoli-Leydig cell tumor of the ovary. A diagnosis of cervical rhabdomyosarcoma in a patient of any age, but especially in young women, should prompt investigation of the patient and her family to determine whether the patient has the syndrome, which is caused by a germline mutation of the *DICER1* gene.

Gross Findings

Cervical rhabdomyosarcomas are mainly polypoid gray-tan or red tumors 1.5–5 cm in maximum diameter (Dehner et al. 2012). Botryoid rhabdomyosarcoma, the most common type in the cervix, is often described as resembling a cluster of grapes. Uterine rhabdomyosarcoma tends to be a polypoid endometrial tumor that grows into the uterine cavity and invades the myometrium. Some rhabdomyosarcomas are nodular tumors located entirely within the myometrium. In one recent series, the average tumor size at presentation was 11.7 cm (Pinto et al. 2018).

Microscopic Findings

Rhabdomyosarcomas of the cervix are more common than those of the uterine corpus, and most are embryonal rhabdomyosarcomas of the botryoid subtype. Botryoid rhabdomyosarcomas are polypoid tumors that have a densely cellular zone of primitive cells beneath the surface epithelium (the "cambium layer") (Fig. 89) (Daya and Scully 1988; Dehner et al. 2012; Li et al. 2013). The substance of the polyps is generally myxoid or edematous, with varying cellularity. It often contains hyperchromatic cellular nodules and zones of hemorrhage. The tumor cells range from undifferentiated small round cells with hyperchromatic nuclei and scanty cytoplasm ("small round blue cells") to strap-shaped cells with eosinophilic cytoplasm. Cells with cross striations are typically difficult to identify. Foci of immature appearing cartilage are admixed with the rhabdomyoblasts in a significant minority of cases. Non-polypoid and infiltrative portions of the tumors are usually histologically indistinguishable from embryonal rhabdomyosarcomas of the usual (non-botryoid) type, with cellular zones that alternate with paucicellular zones with a myxoid or edematous matrix. An unusual botryoid rhabdomyosarcoma that contained areas with a more pleomorphic pattern has been reported (Houghton and McCluggage 2007).

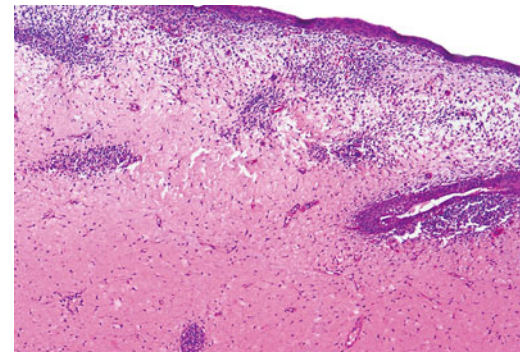

Fig. 89 Botryoid rhabdomyosarcoma. These tumors are typically composed of grape-like tumors with a paucicellular matrix that appears myxoid or edematous. Condensation of primitive cells beneath the overlying epithelium and alongside any entrapped epithelium (so-called cambium layer) is common. Phyllodes-like architecture and intraglandular stromal papillae, seen in adenosarcoma, are lacking

Rhabdomyosarcomas of the uterine body in older patients are often high-grade pleomorphic sarcomas composed of round, polygonal, or spindle-shaped cells admixed with rhabdomyoblasts (Ordi et al. 1997; Pinto et al. 2018). The rhabdomyoblasts range from round cells with prominent perinuclear rims of eosinophilic cytoplasm to spindle- or tadpole-shaped cells with fibrillar eosinophilic cytoplasm.

In the female genital tract, alveolar rhabdomyosarcoma occurs most often in the vulva but also occurs in the uterine body and cervix (Fukunaga 2011; Pinto et al. 2018). The tumor cells tend to be larger than those in embryonal rhabdomyosarcoma. In some tumors round or irregular spaces are surrounded by tumor cells,

resulting in an alveolar appearance. Tumor cells often seem to cling to the conspicuous fibrovascular septae that traverse sheets of tumor cells. In other alveolar rhabdomyosarcomas, tumor cells form a solid mass with no alveolar spaces. Regardless of the growth pattern, the tumor cells have a distinctive cytologic appearance with round nuclei, larger than those in embryonal rhabdomyosarcoma, and scanty cytoplasm. Multinucleated tumor cells are commonly present. Round and spindled cells with brightly eosinophilic cytoplasm are present in most cases and are important clues to the diagnosis. Tumor cells with cross striations can generally be identified.

Immunohistochemistry and Molecular Pathology

The typical immunophenotype includes expression of desmin, muscle-specific actin, myogenin, and MyoD1 (Fig. 90). Staining for these markers is present in greater than 90% of rhabdomyosarcomas (Dehner et al. 2012; Li et al. 2013; Pinto et al. 2018). Desmin and muscle-specific actin are not specific for rhabdomyosarcoma, as positive staining is also found in tissues demonstrating smooth muscle and myofibroblastic differentiation. Myogenin and Myo-D1 are nuclear regulatory proteins that are expressed early in skeletal muscle differentiation. Myogenin is the more widely used of the two. In general, the expression of these markers is negatively correlated with differentiation; nuclear staining is widespread in tumors with numerous differentiated rhabdomyoblasts, but only scattered myogenin positive cells are found in rhabdomyosarcomas composed predominantly of undifferentiated cells with few histologically recognizable rhabdomyoblasts. PAX7 has been proposed as an additional useful marker of rhabdomyosarcoma; it appears most likely to stain embryonal and pleomorphic rhabdomyosarcomas, including some cases that fail to stain for myogenin (Charville et al. 2016).

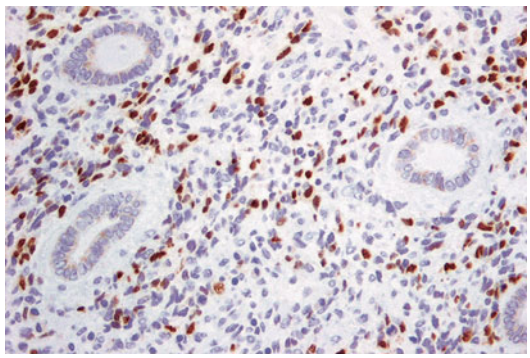

Fig. 90 Botryoid rhabdomyosarcoma. Myogenin expression in tumor cell nuclei confirms rhabdomyoblastic differentiation

Expression of myogenin and Myo-D1 is common to all tumors demonstrating skeletal muscle differentiation, which means that tumors other than pure rhabdomyosarcoma (e.g., adenosarcoma or carcinosarcoma containing rhabdomyoblasts) must be excluded before using myogenin or Myo-D1 immunoreactivity to confirm a diagnosis of rhabdomyosarcoma. Rhabdomyosarcoma may rarely express markers that are more commonly expressed in its histologic mimics, including staining for CD99, cytokeratin, S100 or WT1. Occasional tumors show co-expression of neuroendocrine markers such as chromogranin and synaptophysin along with desmin and myogenin.

Immunohistochemistry may help with the subclassification of rhabdomyosarcoma. Staining for myogenin is likely to be strong and diffuse in alveolar rhabdomyosarcoma; staining is weaker and more focal in embryonal rhabdomyosarcoma (Heerema-McKenney et al. 2008; Morotti et al. 2006). Positive nuclear staining for PAX-5 is reported to be present in about two-thirds of alveolar rhabdomyosarcomas, but staining tends to be absent in embryonal rhabdomyosarcoma (Sullivan et al. 2009). In a limited number of cases with genetic correlation, staining occurred only in tumors that had one of the characteristic translocations, but there was no correlation with a specific translocation.

A majority of alveolar rhabdomyosarcomas exhibit a clonal chromosomal translocation, either t(2;13)(q35;q14), resulting in a *PAX3-FOX01* fusion, or t(1;13) (p36;q14), resulting in a *PAX7-FOX01* fusion. These translocations can be identified using FISH and demonstration of a translocation can support a diagnosis of alveolar rhabdomyosarcoma (Rivasi et al. 2008). There

appears to be a survival difference between patients whose tumors have the *PAX3-FOX01* fusion and those whose tumors have the *PAX7-FOX01* fusion, with the former having a significantly worse prognosis, at least when metastatic disease develops (Sorensen et al. 2002).

Differential Diagnosis

Myxoid leiomyosarcoma may resemble embryonal rhabdomyosarcoma and pleomorphic leiomyosarcoma can appear similar to pleomorphic rhabdomyosarcoma. Embryonal rhabdomyosarcoma, when spindled and growing in fascicles, frequently has a subtle moth-eaten appearance that results from a heterogeneous admixture of cells, some containing densely eosinophilic cytoplasm and others clear or amphophilic cytoplasm (Fig. 91). Round rhabdomyoblasts with bright red cytoplasm are often haphazardly intermixed. The low power appearance of leiomyosarcoma, in contrast, is generally more uniform. Most embryonal rhabdomyosarcomas with an infiltrative, spindle cell appearance underlie a botryoid tumor and/or are clearly epitheliotropic. Leiomyosarcomas, in contrast, are usually more deeply seated lesions. Immunohistochemistry is useful for distinguishing rhabdomyosarcoma from leiomyosarcoma. Diffuse desmin expression is present in both, but only rhabdomyosarcoma shows staining for myogenin.

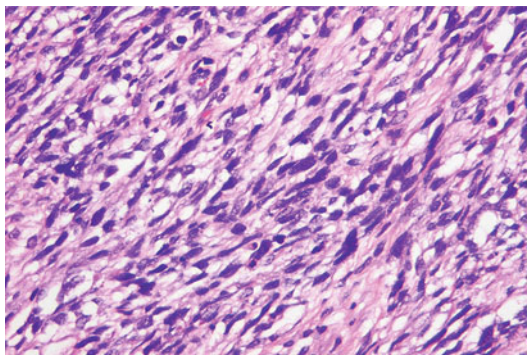

Fig. 91 Rhabdomyosarcomas with spindle cell morphology may mimic leiomyosarcoma. As compared to leiomyosarcomas, rhabdomyosarcomas more frequently lack an eosinophilic appearance at low power and instead demonstrate a subtle moth-eaten look owing to the admixture of round and spindled rhabdomyoblasts

Caldesmon can be positive in leiomyosarcoma but is generally negative in rhabdomyosarcoma.

Adenosarcoma and embryonal rhabdomyosarcoma both show polypoid growth and stromal condensation beneath epithelium, but botryoid rhabdomyosarcoma more typically contains conspicuous myxoid stroma and has a sprinkling of small cellular aggregates of dark blue, primitive and mitotically active cells in a paucicellular background. These features can sometimes be appreciated macroscopically, such that gross inspection of a glass slide can suggest the correct diagnosis. In contrast to adenosarcoma, rhabdomyosarcoma does not exhibit phyllodes-like growth or intraglandular stromal papillae. Adenosarcomas with stromal overgrowth frequently contain rhabdomyoblastic foci and these are the ones most likely to be misdiagnosed as a rhabdomyosarcoma.

Stromal-predominant carcinosarcoma is excluded by a careful search for a malignant epithelial component. The presence of any type of carcinoma indicates that the tumor is a carcinosarcoma. Some genital pleomorphic rhabdomyosarcomas represent carcinosarcomas in which the epithelial component is overgrown by the sarcomatous mesenchymal component.

Pleomorphic undifferentiated sarcoma can resemble rhabdomyosarcoma, as it is composed of mitotically active atypical round or spindle cells. However, rhabdomyoblasts with eosinophilic cytoplasm are not present, and staining for myoid markers such as desmin and myogenin is negative. Undifferentiated and high-grade stromal sarcomas can express CD10, but this marker may not be helpful in the differential diagnosis with pleomorphic rhabdomyosarcoma since some of those also express CD10 (Fadare et al. 2010).

Undifferentiated carcinoma also enters the differential diagnosis as it consists of medium-sized round cells with scanty cytoplasm with no obvious glandular differentiation. Undifferentiated carcinoma may show areas of cellular cohesion, and the tumor cells show at least focal staining for keratin or EMA. Staining for markers of myoid differentiation is absent. Also, many undifferentiated carcinomas are associated with a component of endometrioid adenocarcinoma

somewhere in the tumor, a combination that is referred to as a dedifferentiated carcinoma.

Clinical Behavior and Treatment

Most adult patients are treated surgically, with or without chemotherapy and radiation therapy. In a retrospective review of genital tract rhabdomyosarcoma in adults, the median time to progression was only 9 months and the median disease-specific survival was 21 months; the 5-year disease-specific survival was only 29% (Ferguson et al. 2007). Neither age nor stage correlated with survival. These patients were not offered pediatric therapeutic protocols, which perhaps resulted in unanticipated poor survivals. In this study, embryonal rhabdomyosarcomas appeared to have better survivals compared to other rhabdomyosarcoma subtypes. Other series reporting predominantly pleomorphic rhabdomyosarcomas in older women have also documented poor survivals (Fadare et al. 2010; Ordi et al. 1997; Pinto et al. 2018).

Women with cervical rhabdomyosarcoma have a longer time to progression than women with disease at other gynecologic sites, and women with an embryonal rhabdomyosarcoma have improved progression free survivals compared to those with nonembryonal types of rhabdomyosarcoma (Kriseman et al. 2012; Nasioudis et al. 2017a). In one recent series of botryoid embryonal rhabdomyosarcomas in women having an average age of 44 years, 5 of 7 patients were alive with no evidence of disease (Li et al. 2013).

Children, teenagers, and some young adults with cervical botryoid rhabdomyosarcomas are generally treated by limited excisions such as polypectomies or LEEP excisions to establish the diagnosis, followed by chemotherapy and in some instances radiation. Primary surgical management using fertility sparing techniques is also an option in young women (Bouchard-Fortier et al. 2016). The poor survival statistics for adults with genital tract rhabdomyosarcoma contrasts with the favorable survival rates in children and young women with cervical embryonal rhabdomyosarcomas, most of who appear to be cured by limited surgery and chemotherapy (Daya and Scully 1988; Dehner et al. 2012). It is uncertain whether contrasting clinical outcomes are attributable to intrinsically different biological attributes and/or differences in therapy.

ASPS

ASPS is uncommon in the female genital tract, but it occasionally occurs in the vagina, cervix, or uterus. Uterine tumors have been described in the endometrium, lower uterine segment, and myometrium (Kasashima et al. 2007; Nielsen et al. 1995; Radig et al. 1998; Schoolmeester et al. 2017). The average patient age is about 30 years, and most patients present because of abnormal bleeding.

ASPS is composed of cells with abundant clear-to-eosinophilic cytoplasm that grow in solid nests or, when there is loss of cellular cohesion, an alveolar pattern (Fig. 92). The tumor cell cytoplasm is filled with granules and crystals that are periodic acid–Schiff (PAS)-positive and diastase resistant. Nuclei are usually round with prominent nucleoli. Mitotic activity is low and mitotic figures can be difficult to identify. The fibrovascular framework that supports the nests and alveoli can be conspicuous. The tumors tend to involve the cervical mucosa or endometrium. ASPS that arise in the soft tissues frequently show vascular invasion, but this is uncommon in gynecologic cases.

ASPS are characterized by a chromosomal translocation, t(x;17)(p11;q25), in which the

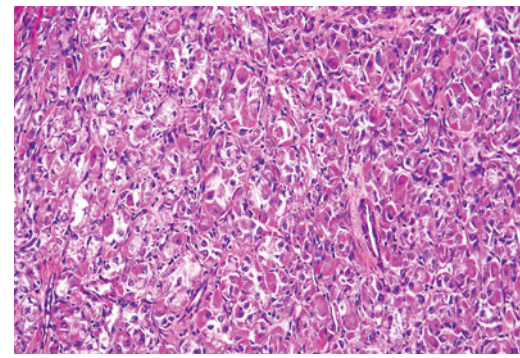

Fig. 92 ASPS. The tumor is formed of nested aggregates of epithelioid tumor cells with granular or crystalline cytoplasm

TFE3 transcription factor gene on chromosome Xp11 is fused to *ASPSCR1* (ASPL) on chromosome17q25 (Ladanyi et al. 2001). An immunohistochemical stain for the TFE3 protein, which is a nuclear antigen, can be used as a diagnostic adjunct to recognize tumors with this translocation (or other abnormalities involving *TFE3*) (Argani et al. 2001; Argani et al. 2003; Kasashima et al. 2007; Roma et al. 2005). TFE3 immunostains should only be interpreted as positive when staining is diffuse and strong in tumor cell nuclei. The presence of the translocation can be confirmed by FISH breakapart probe testing for *TFE3*, by dual color probe FISH testing for the *ASPSCR1-TFE3* fusion, and by molecular testing to identify the fusion transcripts (Jabbour et al. 2014; Schoolmeester et al. 2017). ASPS are mainly negative for markers that stain smooth muscle tumors and PEComas, but rare cases have been reported to show strong but focal staining for HMB45 (Schoolmeester et al. 2017).

The differential diagnosis of ASPS includes adenocarcinoma, epithelioid smooth muscle tumors, PEComa, metastatic melanoma, and a UTROSCT. Adenocarcinoma, epithelioid smooth muscle tumor, metastatic melanoma, and UTROSCT all have a different immunophenotype than ASPS, but the immunohistochemical features of PEComa and ASPS can sometimes be similar. This is because some PEComas express TFE3 (Folpe et al. 2005; Schoolmeester et al. 2015). Any appreciable desmin staining or staining with markers such as HMB-45, MITF, or Melan-A would support PEComa over ASPS.

Gynecologic ASPS has a relatively good prognosis compared to soft tissue ASPS, but the number of cases and the length of follow-up reported are insufficient to draw definitive conclusions. In one series of 9 patients, 1 patient died of tumor and the other 8 were alive with no evidence of tumor 9 months to 17 years after diagnosis (Nielsen et al. 1995). In another series of 10 patients, 4 were alive with no evidence of tumor after short follow-up and the rest were recent cases or lost to follow-up (Schoolmeester et al. 2017). Recently, there has been interest in using MET inhibitors to treat ASPS, since the fusion present in ASPS activates MET signaling, and in blocking the VEGF signaling pathway.

PNET

PNET only rarely arises in the uterus. It can occur at any age, but most are found in postmenopausal women. The median age in the largest series was 58 years, and most patients had stage III or stage IV tumors (Euscher et al. 2008). In another large series the average age of women with uterine PNETs was 51 years (Chiang et al. 2017b). The usual clinical presentation is with abnormal vaginal bleeding.

PNET is a soft, fleshy, gray or white polypoid mass that originates in the endometrium and invades the myometrium. Microscopically, PNET is composed of small cells with round to oval hyperchromatic nuclei and scanty cytoplasm (Fig. 93). Mitotic figures are usually numerous. Evidence of neuroectodermal differentiation includes the presence of an eosinophilic fibrillary background or the formation of rosettes or pseudo-rosettes.

Immunostains are generally positive for one or more neural or neuroendocrine marker and staining

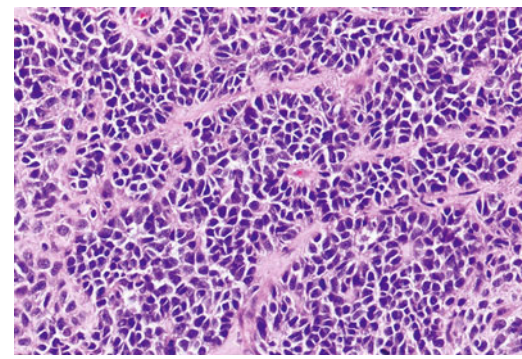

Fig. 93 PNET of the uterus. The tumor is composed of small cells with hyperchromatic nuclei, coarse chromatin, and scanty cytoplasm, arranged in nests and trabeculae. Rosettes or pseudorosettes are seen in some cases. This case was immunoreactive for CD56, chromogranin, and neurofilament

for keratin is generally absent. The most useful immunostains are keratin, which is generally negative excluding a carcinoma, and synaptophysin, glial fibrillary acidic protein (GFAP), and neurofilament, which are usually positive. Staining for other neuroectodermal markers such as chromogranin, neuron-specific enolase, and CD56 is more variable but occasionally one or more are positive. Many uterine PNET, especially those with a t(11;22), express CD99 in a diffuse, membranous pattern, as well as FLI-1. Positive staining for CD99 and FLI-1 is not proof that a tumor is a peripheral type PNET, since central type PNET without evidence of a translocation frequently show CD99 staining (Chiang et al. 2017b; Euscher et al. 2008).

Uterine PNET appear to fall into two categories. Some have a chromosomal translocation, usually t(11;22) resulting in a fusion between the *EWS* and *FLI1* genes. These demonstrate histologic, immunohistochemical, and biologic similarities to Ewing sarcoma (Blattner et al. 2007; Varghese et al. 2006). Other uterine PNET, including all tested uterine tumors in the two largest reported series, lacked evidence of an *EWSR1* rearrangement and are thus more akin to embryonal tumors of the central nervous system, which were previously called central PNET (Chiang et al. 2017b; Euscher et al. 2008).

Mixtures of PNET and other tumor types are occasionally seen. PNET has been reported in association with various types of sarcoma, with carcinosarcoma and adenosarcoma and with endometrioid adenocarcinoma (Quddus et al. 2009; Sinkre et al. 2000a). When associated with carcinosarcoma or adenosarcoma PNET is viewed by some as a form of heterologous differentiation.

Too few patients have been studied to define the clinical behavior and most appropriate treatment for PNET of the uterus. Women with stage I neoplasms can be cured, but more advanced tumors are frequently fatal. In one series 7 of 13 patients with follow-up died of tumor and 6 were alive with no evidence of disease (Euscher et al. 2008), while in another series 2 of 4 patients with follow-up died (Chiang et al. 2017b).

Miscellaneous Mesenchymal Tumors and Conditions

Adenomatoid Tumor

Adenomatoid tumors are distinctive benign genital tract neoplasms of mesothelial origin that occur in both men and women (Nogales et al. 2002). In women they occur in the uterus, the fallopian tube, and the ovary.

Clinical Features

Adenomatoid tumors typically occur in women of reproductive age; the median age is 42 years. There is no evidence that they impair fertility, and they are usually incidental findings in uteri removed for other causes. Adenomatoid tumors are reportedly found in about 1% of hysterectomy specimens, although in a systematic prospective study adenomatoid tumors were found in 5% of hysterectomies and 5% of uterus-preserving tumor excisions, suggesting that they may be more common than is generally appreciated (Nakayama et al. 2013). Adenomatoid tumors are typically thought to be small leiomyomas and, except for rare large cystic tumors, no specific symptoms have been attributed to them (Nogales et al. 2002). Adenomatoid tumors are benign.

Pathologic Findings

Adenomatoid tumors are usually located subserosally in the cornual myometrium. They are typically small, measuring 0.5–1 cm in diameter, but some are larger and giant, and cystic adenomatoid tumors have been reported. Adenomatoid tumors are round and rubbery and are often thought to be leiomyomas. The cut surfaces are gray or tan and may have a spongy appearance due to the presence of uniform small cysts.

Microscopically, adenomatoid tumors tend to be circumscribed, although rare diffuse variants have been described. They consist of tubules and cords of varying size and shape that are lined by flat or cuboidal epithelial cells (Fig. 94). Strands of cytoplasm, so-called thread-like bridging strands, cross the lumens are distinctive finding that is

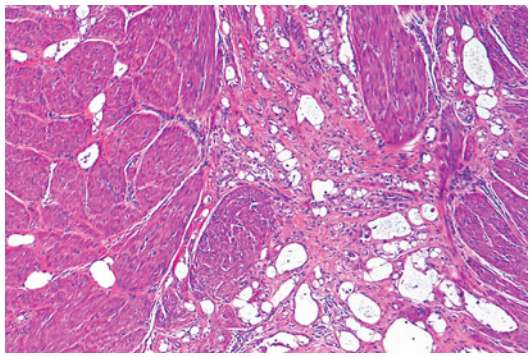

Fig. 94 Adenomatoid tumor within hypertrophic myometrium. Variably sized tubules are lined by flattened or cuboidal mesothelial cells

almost invariably seen in adenomatoid tumors (Sangoi et al. 2009). Collagen, elastic tissue, and smooth muscle surround the epithelial elements. The smooth muscle may predominate such that the tumor appears at first glance to be a leiomyoma or lipoleiomyoma. The cuboidal epithelial cells have cytologically bland, eccentric, round nuclei and abundant pale cytoplasm. The cytoplasm is often vacuolated, sometimes to the extent that some tumor cells resemble signet-ring cells. The growth of the epithelial cells between smooth muscle bundles and the presence of signet-ring-like cells may raise the suspicion of metastatic adenocarcinoma. Nuclear atypia, however, is absent or minimal, mitotic figures are infrequent, and stains for mucin are negative. When the cells lining the tubules are flattened, an adenomatoid tumor may resemble a hemangioma or lymphangioma. However, the lumens do not contain blood, and immunostains for such vascular markers as factor VIII-related antigen and CD 31 are negative. Ultrastructural and immunohistochemical studies reveal that the epithelial cells in adenomatoid tumors have a mesothelial phenotype. Immunostains are positive for cytokeratin and vimentin and for such mesothelial cell-associated antigens as calretinin, WT1, and D2-40 (Sangoi et al. 2009). Stains for adenocarcinoma-associated antigens such as CD 15, CEA, B72.3, and Ber-EP4 are usually negative, and GATA-3 is negative in uterine adenomatoid tumors (Ronaghy et al. 2018), as is PAX8 (Wachter et al. 2011). Lymphoid aggregates are present in some adenomatoid tumors.

Adenomatoid tumors have recently been shown to be clonal proliferations based on non-random x-chromosome inactivation (Wang et al. 2016). Our group recently identified *TRAF7* mutations in all tested examples of adenomatoid tumors of the male and female genital tracts, providing a genetic basis for the tumor (Goode et al. 2018).

Vascular Tumors

Hemangiomas of the uterus, like those at other sites, are composed of neoplastic vessels lined by flat or cuboidal endothelial cells. The endothelial cells have bland nuclei and mitotic figures are rare or, most typically, absent. Uterine hemangiomas can be subclassified as capillary, cavernous, or venous, depending on the appearance of the vessels (Lotgering et al. 1989; Weissman et al. 1993). Rare histologic types of hemangiomas can occur in the uterus, such as Kaposiform hemangioendothelioma and glomeruloid hemangiomas (Giner et al. 2012; Zhang et al. 2012). The subtypes do not differ clinically, except that rare variants like the glomeruloid hemangioma may be a marker for other disease states (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome). Capillary hexmangiomas of the cervix are the most common vascular tumors of the uterus. Most occur in women of reproductive age, and expression of ER and PR in the endothelial cells and stroma suggests that hormonal stimulation may play a part in their growth (Busca and Parra-Herran 2016). The average diameter is about 2 cm. Women with cervical hemangiomas often experience abnormal bleeding and pain. Hemangiomas of the corpus are uncommon (Chou and Chang 2012), and they vary considerably in size. Large hemangiomas can extend through the full thickness of the myometrium and can result in severe bleeding that requires a hysterectomy. Arteriovenous malformations can occur in the uterus (Fleming et al. 1989; Majmudar et al. 1998). They are differentiated from venous hemangiomas by the presence of thick-walled vessels of both arterial and venous types. Histologic distinction between a hemangioma and a vascular malformation can be difficult but is not critical because their clinical features are similar.

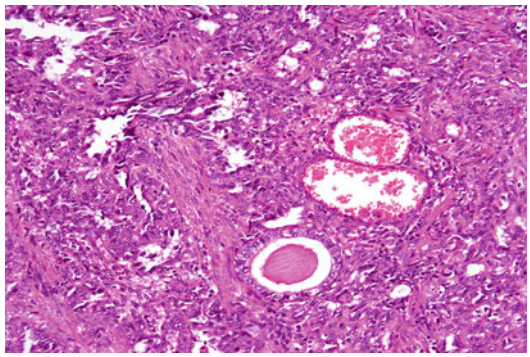

Fig. 95 Angiosarcoma of the uterus. The growth is partly solid but vascular lumens are readily identified. The malignant cells are cuboidal or polygonal and have atypical hyperchromatic nuclei. Numerous mitotic figures were visible at higher magnification. A benign gland is surrounded by tumor (lower center)

A few examples of angiosarcoma of the uterus have been reported (Cardinale et al. 2008; Liu et al. 2016; Schammel and Tavassoli 1998). Angiosarcoma is a large, hemorrhagic, and often extensively necrotic tumor that grows in the myometrium. It consists of anastomosing vascular channels that are lined by atypical cuboidal or "tombstone"-shaped endothelial cells (Fig. 95). Many mitotic figures are usually present. Some high-grade angiosarcomas consist partly or completely of solid sheets of difficult-to-recognize epithelioid endothelial cells. When these cells predominate, the nature of the tumor can be determined by identifying characteristic foci of vascular growth, often at the periphery of the tumor, and by positive immunohistochemical stains for markers of vascular differentiation such as factor VIII-related antigen, CD 31, or ERG. Angiosarcoma extensively invades and replaces the myometrium and has a poor prognosis, with 10 of 15 reported cases dead of disease at a mean of 13 months (Roma et al. 2017). In one review, surgery followed by adjuvant radiotherapy seemed to provide the best treatment results (Kruse et al. 2014b).

Lymphoma

Lymphomas involving the corpus and cervix are discussed in ▶ Chap. 21, "Hematologic Neoplasms and Selected Tumorlike Lesions Involving the Female Reproductive Organs." Accordingly, what follows is brief overview of these disorders. Lymphoma rarely occurs with initial signs or symptoms suggestive of a uterine tumor, but when it does, the cervix is involved more often than is the endometrium (Harris and Scully 1984; Nasioudis et al. 2017b). Most patients are older than 20 years and present with an abdominal or pelvic mass, abnormal vaginal bleeding, a vaginal discharge, or pelvic discomfort. Diffuse large cell lymphomas of B-cell type are most common (Frey et al. 2006; Kosari et al. 2005; Vang et al. 2000). An 80–90% survival rate has been reported for women with localized lymphomas of the uterus and vagina (Ahmad et al. 2014; Vang et al. 2000). The differential diagnosis includes a leiomyoma with a heavy lymphocytic infiltrate and an inflammatory lymphoma-like lesion (pseudolymphoma). Rare leiomyomas contain a heavy lymphocytic infiltrate; however, these are circumscribed tumors containing recognizable areas of residual smooth muscle tumor. Additionally, the lymphocytic infiltrate consists of a mixture of cell types (Botsis et al. 2005; Ferry et al. 1989). Inflammatory "pseudolymphomas" mainly involve the cervical or endometrial surface or are just beneath it, whereas lymphoma is larger and more deeply situated (Geyer et al. 2010; Ma et al. 2007; Young et al. 1985). These lesions consist of a polymorphous inflammatory infiltrate with a mixture of B and T cells and no immunoglobulin light chain restrictions. However, four of nine analyzed cases had clonal rearrangements of the immunoglobulin heavy chain. None of the patients had evidence of a lymphoma on staging or on follow-up, and the authors concluded that in this setting, the clonal immunoglobulin heavy chain rearrangement was insufficient evidence for a diagnosis of lymphoma (Geyer et al. 2010). Uterine involvement as a manifestation of leukemia is very rare (Garcia et al. 2006; Oliva et al. 1997).

Inflammatory processes contain a heterogeneous population of lymphoid cells in contrast to the more monomorphic population seen in most lymphomas, and they are polyclonal. Intravascular lymphocytic accumulations have been described in association with severe chronic

cervicitis. Small and medium-sized non-atypical lymphocytes accumulate in lymphatic channels in these cases and express a mixture of T and B cell phenotypes indicative of a benign condition (Karpathiou et al. 2018).

The differential diagnosis of lymphomas and leukemias also includes neoplastic entities, including small cell carcinoma, undifferentiated carcinoma, and IMT, which are discussed elsewhere in this text.

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