Smooth Muscle Tumors of the Uterus
A Practical Approach
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- Smooth muscle tumors (SMTs) are the most frequent mesenchymal tumors of the uterus. The majority of the uterine SMTs are readily classifiable as benign or malignant based on their gross and microscopic appearances. However, when unusual features are seen in some leiomyoma variants, the differential diagnosis with a leiomyosarcoma may become challenging. Moreover, diagnostic criteria for the different subtypes of leiomyosarcoma are not uniform. Finally, non–smooth muscle tumors that originate in the uterus may show overlapping histologic and even immunohistochemical features with uterine SMTs, more commonly with the spindle and epithelioid variants, complicating their correct classification. The diagnosis of malignant uterine SMTs has important prognostic and therapeutic implications. This review provides a practical approach to the diagnosis of uterine leiomyosarcoma based on a systematic assessment of histologic parameters as well as a systematic approach to its differential diagnosis based on histologic and immunohistochemical features.

 leiomyosarcoma (LMS), the most frequent uterine sarcoma, typically affects women older than 40 years. Patients frequently present with abnormal vaginal bleeding, pain, or both. Rarely, hemoperitoneum due to tumor rupture, extraperitoneal extension, or metastases may be the presenting manifestation. An accurate diagnosis of LMS is relevant, since patients diagnosed with LMS should undergo radical hysterectomy, as surgery is the mainstay of treatment. Furthermore, at the present time there are no established histologic or molecular parameters that predict behavior of LMS, even in stage I tumors. Finally, patients with LMS have a relatively poor 5-year survival rate (20%–75%) and a high recurrence rate (45%–75%), including the absence of nuclear membrane with discernible cytoplasm and the presence of hairy extensions of chromatin extending from a central clotlike dense mass of chromosomes (single clot in metaphase or separate in telophase) (Figure 1). The presence of atypical "mitosis-like" figures in the absence of typical mitoses should alert to the possibility of being confronted with apoptotic cells. Finally, it also is important to keep in mind that mitotic activity in U-SMTs, in contrast to mitotic activity in soft tissues in general, does not possess the same prognostic implications. Although a high mitotic index is acceptable in benign U-SMTs, in contrast to other soft tissues and organ-based SMTs, where any mitotic activity raises high suspicion for malignancy.

MITOTIC ACTIVITY
In the past, the presence of 10 or more mitoses per 10 high-power fields (HPFs) was considered key to establishing the diagnosis of leiomyosarcoma. Even though mitotic index is an important feature in the assessment of malignancy, several studies based on large series of uterine smooth muscle tumors (U-SMTs) have shown that mitotic activity alone is not predictive of poor outcome in these tumors. The classification of U-SMTs proposed by Bell and colleagues has the advantage of downplaying the importance of mitotic rate as a determinant diagnostic feature in malignant U-SMTs, reducing the number of cases diagnosed as leiomyosarcoma that follow a benign course. Assessing mitotic activity in smooth muscle tumors (SMTs) also has been a subject of debate. Apoptotic cells, pyknotic nuclei, lymphocytes, mast cells, and also in non–smooth muscle tumors of the uterus. Some authors recommend the use of strict criteria to identify mitotic figures and have proposed different methods to standardize and thus to increase reproducibility to measure mitotic activity including the use of immunohistochemistry. Criteria for strict mitotic count in hematoxylin-eosin–stained tissue include the absence of nuclear membrane with discernible cytoplasm and the presence of hairy extensions of chromatin from a central clotlike dense mass of chromosomes (single clot in metaphase or separate in telophase) (Figure 1). The presence of atypical "mitosis-like" figures in the absence of typical mitoses should alert to the possibility of being confronted with apoptotic cells.

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Figure 1. Mitotic figure. A cell shows clear cytoplasm and linear extensions of chromatin extending from a central clotlike dense mass of chromosomes (hematoxylin-eosin, original magnification ×400).

Figure 2. Main types of necrosis in smooth muscle tumors. a. Tumor cell necrosis. There is an abrupt transition from viable to nonviable tumor with preserved tumor cells showing perivascular growth. b. Infarct-type necrosis. A zone of fibrosis associated with recent hemorrhage is seen between viable (bottom right) and ghost tumor (upper left) cells. c. Early infarct-type necrosis. Apoptotic smooth cells are intercalated with viable cells and may cause concern for tumor cell necrosis (hematoxylin-eosin, original magnifications ×100 [a, b] and ×200 [c]).

Figure 3. Spindle cell leiomyosarcoma. Cohesive spindle cells form large intersecting fascicles. The tumor is hypercellular, and the cells show marked cytologic atypia (hematoxylin-eosin, original magnification ×100).

Figure 4. Apoplectic leiomyoma. A central area of hemorrhage is surrounded by a more cellular rim of neoplastic smooth muscle cells (arrows). Further away, the tumor becomes less cellular (typical leiomyoma; “zonation phenomenon”; hematoxylin-eosin, original magnification ×2.5).
NUCLEAR ATYPIA
A constellation of cytologic features, including nuclear pleomorphism, hyperchromatism, irregularity in nuclear membranes, high nuclear size, and prominent nucleoli, when present, are indicative of significant atypia. However, cytologic atypia may be overestimated when studying SMTs, and in general any tumor, at high-power magnification. Nuclear atypia must be recognized and taken into account at low-power magnification (×10), comparing it with the nuclear features of the adjacent myometrium when possible.

TUMOR CELL NECROSIS
Tumor cell necrosis is only seen in LMSs. This type of necrosis is defined by finding an abrupt transition from necrotic to nonnecrotic tumor, without interposed granulation or fibrous tissue. Preserved nuclei with marked pleomorphism and hyperchromasia and nuclear debris that are usually lacking inflammation are frequently seen within the necrotic areas. Viable tumor often shows a perivascular growth (Figure 2, a). In our experience, it is extremely rare to find tumor cell necrosis in an LMS in the absence of both cytologic atypia and brisk mitotic activity. In a recent series, we found that of 77 LMSs, including 44 spindle, 22 epithelioid, 6 myxoid, and 5 mixed spindle and epithelioid LMSs, all but 1 tumor showed marked nuclear pleomorphism and more than 10 mitoses per 10 HPFs when tumor cell necrosis was present in the neoplasm.

In contrast to tumor cell necrosis, infarct type necrosis, secondary to ischemia, can occur either in benign or malignant U-SMTs. It is characterized by finding either granulation tissue or hyalinization between the necrotic and nonnecrotic areas, frequently associated with recent hemorrhage. The necrotic areas have a mummified appearance showing ghost outlines of the tumor cells, and both tumor and vessels appear dead (Figure 2, b). The end result is the replacement of the infarcted area by dense hyalized tissue. It is important to keep in mind that when necrosis is seen at an early stage, the microscopic features just described are typically absent, and in those instances it may be very difficult to distinguish infarct from tumor cell necrosis. Furthermore, very early infarct type necrosis, characterized by single apoptotic cells admixed with viable cells, may also be confused with tumor cell necrosis (Figure 2, c). Thus, it is always very important to evaluate cytologic atypia and mitotic activity. If tumor cell necrosis is present in a tumor, it is almost always accompanied by cytologic atypia and brisk mitotic activity. Ulcerative necrosis often seen on the surface of a U-SMT is associated with inflammatory cells, and it is easy to distinguish from the other types of necrosis.

Potential Pitfalls
- Apoptotic cells can be confused with atypical mitoses.
- High-power scrutiny may mislead to identification of inexistent nuclear atypia.
- Early necrosis may be difficult to classify as either tumor or infarct-type.

Recommendations
- Cytologic features should be evaluated at ×10 magnification.
- Cytology of tumor cells should be compared with non-tumoral smooth muscle.
- Caution is required in interpreting “atypical mitoses” as such in the absence of conventional mitotic figures.
- Evaluation of “early” non-well-characterized necrosis should be made in conjunction with nuclear atypia and mitotic activity.
- Perform extensive sampling when unusual features are present in a U-SMT.

The finding of any 1 of these 3 key features (mitotic activity, nuclear atypia, and tumor cell necrosis) in a U-SMT should be taken seriously, but a single feature is neither necessary nor sufficient to establish a diagnosis of malignancy.

LEIOMYSARCOMA: DIAGNOSTIC CRITERIA
The criteria to establish a diagnosis of malignancy in a U-SMT differ for each subtype, increasing the difficulty in diagnosis and reproducibility among pathologists. These can be summarized as follows:

1. Conventional (Spindle Cell) LMS
On microscopic examination, spindle cell LMS is typically composed of elongated cells with eosinophilic fibrillar cytoplasm and elongated blunt-ended nuclei. The cells form long intersecting fascicles and frequently display an infiltrative growth into the surrounding myometrium (Figure 3). Variable degrees of atypia (often moderate to marked) and variable mitotic activity (typically brisk) with or without tumor cell necrosis are identified. The tumors are frequently hypercellular, but they can be normocellular or hypocellular. Rarely conventional LMSs can have osteoclast-like giant cells or xanthomatous cells disposed in sheets or admixed with the spindle smooth muscle cells. In this LMS subtype, the diagnosis of malignancy is established when any 2 of the following 3 criteria are present:
- Diffuse moderate to marked cytologic atypia.
- Mitotic rate 10 or more mitoses per 10 HPFs.
- Tumor cell necrosis.

Additional findings, such as hypercellularity, atypical mitoses, vascular invasion, or infiltrative borders, are seen in most conventional LMSs, but they are not considered diagnostic criteria of malignancy.

Differential Diagnosis
The distinction between spindled cell LMS and some leiomyoma (LM) variants may be quite difficult but crucial, as it carries important therapeutic and prognostic implications. Leiomyoma variants, although uncommon, have an overall higher frequency compared with LMS, simply because LM is the most common neoplasm of the female genital tract, present in about 40% of women older than 50 years and in up to 75% of hysterectomy specimens. Clinically, LMs may cause pelvic pain, abnormal vaginal bleeding, and rapid uterine enlargement, symptoms that overlap with those seen in LMS. Typical LM is readily distinguished from LMS on gross and microscopic examination in most instances. However, there are some LM variants that may display worrisome gross or microscopic features, raising the possibility of malignancy. Those include (1) mitotically active LM; (2) LMs with hormone-related changes, including apoplectic LM; (3) LM with bizarre nuclei; and (4) cellular and highly cellular LM.
Mitotically Active LM Versus Conventional LMS.—This LM variant is defined by the finding of brisk mitotic activity in an otherwise typical LM that occurs in women in their reproductive age, associated with the secretory phase of the menstrual cycle, pregnancy, or the use of exogenous hormones. Grossly, the majority of mitotically active LMs are submucosal with a typical gross cut surface in contrast to LMS, which is intramural in two thirds of cases and frequently has a heterogeneous cut surface. The most important criterion to establish the diagnosis of mitotically active LM (or LM with increased mitotic index) is the absence of cytologic atypia or, at most, the presence of mild nuclear atypia when scanning the tumor at \( \times 10 \) magnification. These tumors often have more than 10 mitoses per 10 HPFs (between 5 and 15, or even 19 in one series). Moreover, mitoses are usually “typical,” but exceptional abnormal mitotic figures are allowed. Ulcerative necrosis and inflammation with reactive changes but no tumor cell necrosis can be observed in a submucosal, mitotically active LM. In the absence of cytologic atypia and tumor cell necrosis, an increased mitotic index up to 20 mitoses per 10 HPFs has no prognostic significance. As mitotically active LMs with more than 20 mitoses per 10 HPFs are extremely rare, tumors in this category may be classified as “leiomyoma with increased mitotic activity, but experience limited.” However, other authors prefer to include these tumors in the group of U-SMT of uncertain malignant potential.

Potential Pitfalls

- Mitotic activity more than 10 per 10 HPFs.
- Cytologic atypia associated with superficial ulceration.

Helpful Clues

- Minimal to absent cytologic atypia with a \( \times 10 \) objective.
- Homogeneous bland appearance.

Applectic LM Versus Conventional LMS.—This is a distinctive U-SMT characterized by multifocal areas of recent hemorrhage that occurs in women in reproductive age either taking oral contraceptives or who are pregnant or recently postpartum. This clinical scenario contrasts with that seen in LMS, which occurs more commonly in postmenopausal women. However, the presenting symptoms may be similar to those encountered in LMS. On gross examination, there are small and frequently multiple hemorrhagic areas that may be accompanied by cystic change. Microscopically, this LM variant is characterized by patchy zones of recent hemorrhage juxtaposed to areas of hypercellular smooth muscle (Figure 4). Secondary to ischemia, the smooth muscle cells in these areas may show dense eosinophilic cytoplasm, enlarged nuclei, plump nuclei, and brisk mitotic activity (as high as 8 mitoses per 10 HPFs), and they may be focally associated with a myxoid background, features that may raise concern for malignancy. However, the average mitotic count is typically low (<2 mitoses per 10 HPFs) and, most importantly, there is a “zonation” phenomenon, whereby further away from these areas the cellularity decreases and the overall cytologic appearance is that of a conventional LM (Figure 4).

Finally, some LMs treated with gonadotrophin-releasing hormone analogs (GnRHAs) given to reduce the size of the LMs prior to their removal may show infarct necrosis in the absence of increased mitotic index or atypia. However, it is important to keep in mind that the same LM removed several weeks after withdrawal of the GnRH treatment can show increase mitotic activity. Clinical information is essential to avoid the misdiagnosis of LMS.

Potential Pitfalls

- Hemorrhagic areas with cystic change.
- Increased cellularity with cytologic atypia and increased mitotic activity.
- Focal myxoid background.

Helpful Clues

- “Zonation” phenomenon from cellular areas next to hemorrhage to distant areas, with appearance of conventional LM at low-power examination.
- Evaluate mitotic rate and cytologic atypia in areas far away from hemorrhage.

LM With Bizarre Nuclei Versus Conventional LMS.—Worrisome features that can be seen in LM with bizarre nuclei include large atypical mononucleated or multinucleated cells, karyorrhectic nuclei, prominent nucleoli, nuclear pseudo-inclusions, coarse chromatin, or even increased mitotic activity by the highest count (up to 7 mitoses per 10 HPFs). On microscopic examination, an important clue to this diagnosis is the patchy or multifocal distribution of the bizarre cells in the tumor (Figure 5, a). However, in rare cases, cells with bizarre nuclei may have a diffuse distribution, and karyorrhectic nuclei may mimic atypical mitoses, raising even more concern for LMS (Figure 5, b). Other helpful features to distinguish LM with bizarre nuclei from LMS include bland cytologic appearance of the smooth muscle cells in areas without bizarre nuclei, low average mitotic account (<2 mitoses per 10 HPFs), and absence of tumor cell necrosis. Ancillary techniques, such as ploidy, MIB-1 activity, and p53 expression, also may be used. Distinction between the two entities is of paramount importance, as LM with bizarre nuclei has an excellent prognosis, including tumors that are only treated with myomectomy.

Potential Pitfalls

- Mononucleated or multinucleated cells with bizarre nuclei.
- Diffuse distribution of atypical cells within the tumor.
- Karyorrhectic nuclei mimicking atypical mitoses.
- Mitotic rate up to 7 mitoses per 10 HPFs by highest count.

Helpful Clues

- Minimal or no cytologic atypia in background non–bizarre smooth muscle cells.
- Dense eosinophilic cytoplasm and clumpy-coarse chromatin indicative of apoptosis.
- Average mitotic rate of 1 to 2 mitoses per 10 HPFs.
- Absence of tumor cell necrosis.

Highly Cellular LM Versus Conventional LMS.—Highly cellular LM may be confused with LMS because of its marked cellularity and, furthermore, it may show an increased mitotic activity or even bizarre nuclei. However, it typically lacks cytologic atypia and tumor cell necrosis, and in most cases the mitotic activity is very low.

Others.—Rarely undifferentiated endometrial sarcoma and spindle cell rhabdomyosarcoma should be considered in the differential diagnosis of spindle LMS. The former is a diagnosis of exclusion, whereas the latter shows cells with bright eosinophilic cytoplasm, which at least should
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Figure 5. Leiomyoma with bizarre nuclei. a, Bizarre mononucleated and multinucleated cells with a patchy distribution are present in a background of smooth muscle cells with bland cytologic features. b, Bizarre cells have a diffuse distribution and show hyperchromatic irregular nuclei resembling atypical mitoses (arrows) mimicking a leiomyosarcoma (hematoxylin-eosin, original magnifications ×125 [a] and ×200 [b]).

alert to search for cross-striations and perform immunohistochemical stains for skeletal markers.37,38

2. Myxoid LMS

This unusual variant of LMS frequently displays a jellylike cut surface with infiltrative borders (Figure 6, a), but it may have deceptive well-delineated margins. On microscopic examination, these tumors are hypocellular, in contrast to most spindle LMS, the cells being embedded in an abundant weakly basophilic myxoid matrix (Figure 6, b) strongly positive with Alcian blue and colloidal iron stains.39 The neoplastic cells may be uniformly distributed throughout the myxoid matrix or arranged in loose fascicles. They have scant cytoplasm, oval, spindle, or stellate nuclei with small nucleoli,10,40 and not infrequently only exhibit focal mild to moderate atypia (Figure 6, b) and low mitotic rate (0–2 per 10 HPFs).39,41 Helpful features to establish the diagnosis of malignancy include the finding of high-grade areas, conventional areas of LMS, irregular infiltration of the myometrium (Figure 6, a), and venous invasion.40–42 Because identification of marked nuclear atypia, tumor cell necrosis, and high mitotic rate is not as frequently encountered in myxoid LMS compared with spindle LMS, despite its malignant course, the consensus diagnostic criteria for this specific variant include:36,41,45

1. Severe cytologic atypia and/or tumor cell necrosis, with any mitotic index.
2. In the absence of atypia or tumor cell necrosis, the finding of 2 or more mitoses per 10 HPFs.

Differential Diagnosis

Myxoid LM Versus Myxoid LMS.—Myxoid change occurs in about 2% of LMs, but this change is rarely extensive and is frequently seen near the zone of repair of an organizing infarct.11,15 Grossly, both myxoid LM and LMS show a soft, gray, gelatinous cut surface, and often a well-circumscribed border.39,41 On microscopic examination, myxoid LM is well demarcated, but the presence of alternating myxoid and nonmyxoid areas in an LM may be misinterpreted as an infiltrative margin into the myometrium. It is very important to rely on the low-power scrutiny to identify the real margin of the tumor. It is even more important to sample the tumor very extensively in order to find areas with more pronounced atypia or mitotic activity.39 Finally, when facing a U-SMT with myxoid and nonmyxoid areas, the latter usually exhibit higher nuclear atypia and mitotic activity in an LMS.10,11,41 As most myxoid LMs have been large tumors (average >10 cm), any myxoid tumor more than a few centimeters in size, with any mitotic activity, or with an infiltrative margin is best regarded as potentially aggressive.2 Distinction between myxoid LM and myxoid LMS may be difficult in curettage specimens or when performing a frozen section due to limited sampling,39 and in these cases the final diagnosis should be deferred.

Potential Pitfalls

● Well-demarcated margin on gross examination.
● Hypocellularity, minimal atypia, and low mitotic activity.
● Alternating myxoid and nonmyxoid areas in an LM misinterpreted as invasion.

Helpful Clues

● Extensive sampling.
● Low-power examination allows recognition of the well-circumscribed interphase.
● In absence of tumor cell necrosis or severe cytologic atypia, a mitotic index of 2 or more per 10 HPFs is key to the diagnosis of myxoid LMS.

Hydropic LM Versus Myxoid LMS.—Generally, hydropic degeneration in LMs is focal and associated with hyalinization.2,46 However, sometimes hydropic change may be extensive and present beyond the confines of the LM, simulating the infiltrative border of a myxoid LMS.11,46 Whereas hydropic degeneration appears as watery, pale, eosinophilic fluid (Figure 7, a), myxoid matrix is basophilic and could be identified by staining for acidic mucins (colloidal iron and Alcian blue).11,15. It is important to keep in mind that a rapidly growing mass in the uterus is frequently interpreted by the clinician as a malignant tumor. Thus, not infrequently, a clinician may ask for an intraoperative consultation. In some cases, these tumors may have a gross appearance that may overlap with that seen in myxoid smooth muscle tumors (Figure 7, b). However, in most cases, the uniform white-gray gross appear-

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Figure 6. Myxoid leiomyosarcoma. a. The tumor has an infiltrative growth pattern into the myometrium. b. The tumor is hypocellular, the cells show minimal atypia, and there is abundant myxoid matrix (hematoxylin-eosin, original magnifications ×20 [a] and ×100 [b]).

Figure 7. Hydropic leiomyoma. a. Benign smooth muscle tumor cells are separated by abundant edematous fluid (hematoxylin-eosin, original magnification ×100). b. The tumor shows a pale “jellylike” cut section resembling a myxoid smooth muscle tumor (gross picture).

Figure 8. Epithelioid leiomyosarcoma. a. A solid/nested growth of epithelioid cells with eosinophilic or clear cytoplasm is seen. b. The tumor cells form anastomosing cords and trabeculae in a hyalinized and edematous stroma (hematoxylin-eosin, original magnification ×100).
ance of the tumor oozing watery fluid even more when it is squeezed is helpful to establish the diagnosis of hydropic LM. If the tumor is myxoid and the representative frozen section does not show obvious features of malignancy, it is best to indicate the myxoid nature of the tumor to the surgeon and defer the final interpretation after extensive sampling has been performed.

Potential Pitfalls

- Hydropic change extending outside the LM may be interpreted as invasion.

Helpful Clues

- Gross appearance includes oozing watery fluid.
- Edematous areas alternating with areas of hyalinization.
- Negative Alcian blue and colloidal iron.

Myxoid Endometrial Stromal Tumors Versus Myxoid LMS.—Myxoid LMS must be differentiated from endometrial stromal sarcoma with myxoid change, as both share prominent myometrial infiltration and intravascular growth.\(^{10,47,48}\) In these cases, the multinodular or tongue-like pattern of infiltration of the myometrium, focal areas of typical endometrial stromal tumor with characteristic arterioles and frequent negativity for smooth muscle markers, are useful criteria for the diagnosis of endometrial stromal sarcoma.\(^{10,11,15,47–49}\) However, it is important to keep in mind that myxoid LMSs may show lesser degrees of positivity for smooth muscle markers than conventional LMS and that U-SMT in general and LMS in particular frequently express CD10.\(^{50}\)

Intravenous Leiomyomatosis Versus Myxoid LMS.—Although LMS can show prominent intravascular growth similar to that encountered in intravenous leiomyomatosis with myxoid change,\(^{51}\) the presence of a fleshy myometrial mass, any degree of cytologic atypia, and mitotic index is indicative of LMS.\(^{2,10,12,24,51,52}\)

3. Epithelioid LMS

This LMS subtype is defined by the finding of rounded to polygonal cells in more than 50% of the tumor.\(^{53–55}\) Grossly, epithelioid U-SMTs may lack a whorled cut surface and may have a softer and tan cut surface compared with conventional SMTs. On microscopic examination, the epithelioid cells have round nuclei and eosinophilic (in approximately 75% of cases) and less frequently vacuolated or clear cytoplasm.\(^{55–57}\) Tumoral cells often show a diffuse growth pattern (Figure 8, a) but can also be disposed in clusters or anastomosing cords and trabeculae, with a varying degree of hyalinization or edema in the background stroma (Figure 8, b).\(^{50,53,57,58}\) Even though in the past these tumors were designated based on their microscopic appearance as leiomyoblastoma,\(^{53,59}\) clear cell, and plexiform epithelioid SMTs,\(^{53}\) we prefer to use epithelioid U-SMT as a unifying term to avoid possible confusion. The term plexiform tumorlet is only used for tumors with a plexiform architecture that measure more than 1 cm.\(^{30,60,61}\) As epithelioid U-SMTs are infrequent, criteria predictive of malignant behavior are less well established than for conventional LMS. In the four largest reported series,\(^{33,53,57,58}\) criteria applied to define an epithelioid SMT of low-malignant potential.\(^{2,24}\) Thus, as a general rule, extensive sampling in any unusual SMT is very important to be able to unmask these features.\(^{24}\)

Differential Diagnosis

Primary poorly differentiated endometrial or metastatic carcinoma, PEComa, uterine tumor resembling an ovarian sex cord–like tumor, tumors derived from intermediate trophoblast (placental site trophoblastic tumor and epithelioid trophoblastic tumor), and melanoma are the main entities to be considered in the differential diagnosis of epithelioid U-SMTs. Rarely, epithelioid endometrial stromal sarcoma, alveolar soft part sarcoma, epithelioid angiosarcoma, pleomorphic rhabdomyosarcoma, or rhabdoid tumor may enter in this differential diagnosis.\(^{10,11,24}\)

Poorly Differentiated Carcinoma (Primary or Metastatic) Versus Epithelioid LMS.—Cells in epithelioid LMS show a cohesive growth, abundant cytoplasm, and round nuclei and may display a signet-ring cell appearance, features that overlap with those seen in poorly differentiated carcinomas.\(^{8,63}\) Most carcinomas, however, exhibit, at least focally, glandular or squamous differentiation, the differential diagnosis being more problematic in a biopsy or curettage specimen, as foci of typical carcinoma may not have been sampled. Finally, when an epithelioid U-SMT shows striking plexiform architecture, the appearance may closely imitate the “indian-file” growth characteristic of metastatic breast carcinoma, more often lobular type.\(^{24,64}\) Immunohistochemical studies may be helpful, especially using a panel of antibodies rather than a single antibody, as epithelioid U-SMTs are frequently positive for cytokeratins and epithelial membrane antigen (EMA)\(^{65}\) and express less frequently muscle markers compared with conventional LMS.\(^{10,11,50,64}\)

Potential Pitfalls

- Diffuse cohesive architecture with scant intervening stroma.
- "Cordlike" pattern simulating metastatic breast carcinoma.
- Frequent positivity for keratin and EMA.
- Negative staining for smooth muscle markers.

Helpful Clues

- Extensive sampling allows identification of foci of well-differentiated carcinoma.
- Exclusive positivity for epithelial markers.

PEComa Versus Epithelioid LMS.—The perivascular epithelioid cell tumor (PEComa) is a relatively newly described low-grade mesenchymal tumor first described in the uterus by Pea and colleagues\(^{66}\) in 1996. It belongs to the family of lesions that originate from the perivascular epithelioid cell (PEC). The PEC has abundant clear to eosinophilic granular cytoplasm and shows positive staining for melanocytic markers with variable expression of smooth muscle markers.\(^{66,67}\) The tumor shows a particular association with lymphangioleiomyomatosis and tuberous sclerosis.\(^{65–70}\) PEComa usually presents as a solitary mass that may either be well circumscribed or show infiltrative growth, as it may occur in epithelioid LMS.\(^{67,69–71}\) On microscopic examination, PEComas show overlapping fea-
tures with epithelioid U-SMTs, as they have cells with abundant clear or eosinophilic cytoplasm and round to oval nuclei arranged in sheets, small solid nests, or cords separated by scant hyalinized stroma (Figure 9, a).67,69,72,73 Spindled areas can also be seen with the cells having elongated nuclei.67,69 Furthermore, recent studies have shown expression of HMB-45 in uterine tumors, including LMs, epithelioid LMSs, and even in normal myometrium.54,58,72,74 Because of these overlapping histologic and immunohistochemical features, there has been some debate in the literature about the origin of PEComa. While some authors agree that PEComa is a true entity,62,69,70,72 other investigators argue that it belongs in the category of SMTs.53,58,73-75 Features that will favor the diagnosis of PEComa over an epithelioid U-SMT include the association with tuberous sclerosis and lymphangiomyomatosis,67-69 the presence of multinucleated giant cells and “spiderlike” cells in PEComa,66 and the expression of HMB-45 (Figure 9, b), Melan A, and MiTF67,72

**Potential Pitfalls**
- Epithelioid cells and diffuse growth.
- Focal spindle cell component.
- Thick blood vessels.
- Positivity for smooth muscle markers.

**Helpful Clues**
- Delicate capillary network absent in epithelioid SMT.
- Presence of multinucleated giant cells and spiderlike cells lacking in epithelioid U-SMTs.
- HMB-45 but not Melan A expressed in epithelioid U-SMTs.
- Frequent keratin and EMA expression in epithelioid U-SMTs but none in PEComa.

**Uterine Tumor Resembling an Ovarian Sex Cord Tumor Versus Epithelioid LMS.**—Uterine tumors resembling ovarian sex cord tumors (UTROSCT) are rare stromal tumors showing massive sex cord–like differentiation.79 On gross examination they may resemble an epithelioid U-SMT due to their yellow cut surface and soft consistency. On microscopic examination, the neoplastic cells show an epithelioid appearance with indistinct eosinophilic (sometimes vacuolated) cytoplasm and oval to round nuclei and grow in tight nests, cords, and sheets76 (Figure 9, c). Sometimes, spindle-shaped cells are present, and the stroma is generally sparse with some hyaline strands, features closely mimicking the appearance of epithelioid U-SMT.76-78 Furthermore, up to one third of UTROSCTs express smooth muscle markers, and they also express epithelial markers, including keratin in up to 50% and EMA in 10% of cases,76,79 a coexpression pattern also observed in epithelioid U-SMTs. However, the overall degree of epithelial differentiation in most UTROSCTs is more pronounced than in epithelioid U-SMTs, with tubular formation, retiform differentiation, or prominent vacuolated cytoplasm, as seen in the luteinized cells of sex cord stromal tumors of the ovary. The absence of sex cord stromal markers (inhibin and calretinin; Figure 9, d) in epithelioid LMS is helpful in this differential diagnosis.50,76-80

**Potential Pitfalls**
- Nests, cords, and trabeculae with minimal intervening stroma.
- Positivity for epithelial and smooth muscle markers.

**Helpful Clues**
- Architectural patterns resembling sex cord stromal tumors of the ovary.
- No clearcut spindle component.
- In approximately half of cases, positivity for inhibin, calretinin, or Mart-1.

**Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor Versus Epithelioid LMS.**—Malignant trophoblastic neoplasms of the intermediate trophoblast are typically seen in reproductive-age women with history of a recent pregnancy.81 Microscopically, placental site trophoblastic tumors (PSTTs) and epithelioid trophoblastic tumors (ETTs) are composed of mononucleated round or polyhedral intermediate trophoblastic cells with abundant eosinophilic to clear cytoplasm frequently associated with a diffuse or nested growth (Figure 9, e).81,82 Features favoring a diagnosis of trophoblastic tumor include history of recent pregnancy or abortion and an elevated serum human chorionic gonadotropin level,83 an infiltrative growth of single cells or small aggregates of cells dissecting individual muscle fibers (PSTT; Figure 9, e), prominent vascular involvement with associated fibri-noïd change (PSTT),82 islands or nests of cells surrounded by extensive necrosis or a hyaline-like matrix (ETT),84 as well as immunoreactivity for inhibin (Figure 9, f), human placental lactogen, and p63 (ETT), with negativity for smooth muscle markers.17,85-89

**Potential Pitfalls**
- Infiltrative growth (PSTT).
- Positivity for epithelial markers.

**Helpful Clues**
- Relevant clinical history.
- Prominent vascular replacement (PSTT).
- Prominent hyaline-like matrix (ETT).
- Positivity for inhibin and human placental lactogen.

**Endometrial Stromal Sarcoma Versus Epithelioid LMS.**—Cells with abundant dense eosinophilic cytoplasm have been rarely described in endometrial stromal tumors, and this finding may lead to favor strongly the diagnosis of an epithelioid U-SMT, especially in small samples.80 In these cases, the morphologic and immunohistochemical features described above in the differential diagnosis between myxoid stromal sarcoma and LMS can be applied.50,80 Another potentially helpful feature is that epithelioid LMS exhibit more cytologic atypia than that typically present in endometrial stromal sarcomas.

**Metastatic Melanoma Versus Epithelioid LMS.**—Although unusual, metastatic melanoma from other genital or extragenital sites could involve the uterus81,82 and should always be in the differential diagnosis of an epithelioid neoplasm. Positivity for S100, HMB-45, and Mart-1, and negative expression of smooth muscle markers will favor the diagnosis of melanoma.11

**Alveolar Soft Part Sarcoma Versus Epithelioid LMS.**—Although alveolar soft part sarcoma of the female genital tract is uncommon, the presence of cells with abundant pale cytoplasm with a solid or nested growth may resemble an epithelioid U-SMT.90 However, a typical alveolar growth and PAS-positive diastase-resistant granules and crystals are not seen in epithelioid U-SMTs, whereas alveolar soft part sarcoma rarely shows a spindle cell component.94 Immunohistochemical stains for smooth muscle markers are of no help, as both tumors are positive, the
Figure 9.  

a, PEComa. Nests of epithelioid clear cells are separated by delicate collagenous septa.  
b, The tumor cells show diffuse and strong HMB-45 expression.  
c, Uterine tumor resembling an ovarian sex cord tumor. A predominant solid growth pattern mimics an epithelioid smooth muscle tumor.  
d, The tumor cells are positive for inhibin.  
e, Placental site trophoblastic tumor. Sheets of round cells with eosinophilic cytoplasm diffusely infiltrate the myometrium.  
f, The tumor cells show intense immunoreactivity with inhibin (hematoxylin-eosin, original magnifications ×200 [a and c] and ×100 [e]; immunostain, original magnifications ×100 [b, d, and f]).
most helpful marker being TFE3, which is only expressed in alveolar soft part sarcoma.80,85

Rhabdoid Tumors and Epithelioid LMS—Some epithelioid LMSs exhibit a rhabdoid phenotype,24 which should be distinguished from pure rhabdoid tumors, pleomorphic rhabdomyosarcomas, or even angiosarcomas of the uterus with an epithelioid morphology.37,38,96 Immunohistochemistry may be needed in this differential diagnosis.38,57,97

GENERAL RECOMMENDATIONS

1. Extensive sampling is recommended for any U-SMT with unusual gross appearance (at least one section per centimeter).

2. The diagnostic criteria for malignancy vary for the different subsets of LMS, but they always include mitotic index, cellular atypia, and presence of tumor cell necrosis.

3. Diagnostic criteria to establish the diagnosis of LMS should be strictly applied.

4. Diagnosis of conventional (spindle) LMS is established when any 2 of the following 3 criteria are present: (1) diffuse moderate to marked cytologic atypia, (2) mitotic rate of 10 or more mitoses per 10 HPFs, and (3) tumor cell necrosis.

5. Diagnosis of myxoid LMS is established when there is (1) severe cytologic atypia and/or tumor cell necrosis with any mitotic index or (2) 2 or more mitoses per 10 HPFs in the absence of atypia or tumor cell necrosis.

6. Diagnosis of epithelioid LMS is established when there is (1) any degree of cytologic atypia and 5 or more mitoses per 10 HPFs in the absence of tumor cell necrosis or (2) 5 or more mitoses per 10 HPFs and tumor cell necrosis with any degree of cytologic atypia.

7. Always exercise caution in reaching a definitive diagnosis of malignancy in a curettage specimen or intraoperative consultation.

8. Clinical information plays an important role (pregnancy or menstrual status, exogenous intake of hormones, others) in the final pathologic interpretation.

9. A panel of antibodies rather than a single antibody should be used when the differential diagnosis is between U-SMTs and their mimics.

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References


