Smooth Muscle, Endometrial Stromal, and Mixed Müllerian Tumors of the Uterus

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UTERINE SMOOTH MUSCLE NEOPLASMS

In most instances, the clinical behavior of uterine smooth muscle neoplasms can be reliably predicted by application of conventional gross and light microscopic features. Problems arise in diagnosis and classification when there is discordance between morphology and clinical outcome. Although, in aggregate, these problematic cases represent a small minority of uterine smooth muscle neoplasms, it is this group that accounts for the notorious difficulty in reliably predicting clinical outcome for some patients with uterine smooth muscle neoplasms. The tumors that present difficulties usually fall into one or more of the following groups: (1) They are clinically benign neoplasms with a peculiar gross appearance, (2) they are clinically benign neoplasms with an unusual anatomic distribution such as within vessels, (3) they are clinically benign neoplasms with aberrant cytologic features, (4) they are clinically benign neoplasms with high mitotic counts, (5) they are clinically malignant but have benign morphologic features, or (6) they are lesions whose smooth muscle differentiation is not obvious.

Historical Review

Although it would be ideal to have a single morphologic feature that would sharply distinguish between clinically benign and clinically malignant uterine smooth muscle tumors, each of the predictors that have been tested during the past half-century fails to forecast correctly clinical behavior in a significant number of problematic cases when used in a univariate fashion. The most commonly used predictors are the number of mitotic figures, atypia, and tumor cell necrosis (1, 2).

The importance of mitotic figures in evaluating smooth muscle tumors of the uterus was well established a quarter of a century ago by Taylor and Norris (2), but it soon became apparent that some uterine smooth muscle neoplasms with relatively low mitotic indices (5 to 10 mitotic figures [mf] per 10 high-power fields [hpf]) were capable of behaving in a clinically aggressive manner and that not all tumors with a mitotic index greater than 10 mf/10 hpf were clinically malignant. The term *smooth muscle tumor of uncertain malignant potential* was created for the 5 to 9 mitotic index group to reflect the uncertainty about the true failure rate in this group (1, 3–6).

Although most clinically aggressive smooth muscle tumors demonstrate cellular atypia, there also exists a small group of clinically benign smooth muscle neoplasms with marked cellular atypia. These have been variously referred to in the literature as “symplastic leiomyoma,” “atypical leiomyoma,” or “bizarre leiomyoma” (1, 7).

The significance of coagulative tumor cell necrosis in the evaluation of uterine smooth muscle neoplasms of the usual or standard histologic type was recently established in a large series of 215 smooth muscle tumors (1), but even in this study, there was a group of clinically aggressive smooth muscle neoplasms without this feature.

The conclusion that must be reached by each of these disparate observations is that no single morphologic feature clearly separates uterine smooth muscle tumors into good and bad actors, but this goal can be achieved using a classification rule that incorporates several morphologic features. Thus, any uniform, reproducible, and clinically relevant classification scheme requires the incorporation of multiple histologic features. The need for a multivariate approach was most recently addressed by Bell *et al.* (1), who proposed a classification system for uterine smooth muscle neoplasms exhibiting standard features (see below) that takes into account the mitotic index, cellular atypia, and the presence or absence of coagulative tumor cell necrosis. The definition of each of these three morphologic features must be adhered to if their predictive power is to be fully realized. Another point must be made: The predictors that best forecast the potential of uterine smooth muscle tumors may not

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accurately predict the behavior of extrauterine smooth muscle tumors. In other words, the morphologic predictors for smooth muscle tumors are highly site specific.

Determining the Direction of Differentiation

Before the prognostic features of a purported smooth muscle proliferation of the uterus are evaluated, it is imperative to ascertain that the constituent cells do indeed demonstrate evidence of smooth muscle differentiation. For most smooth muscle tumors, this is a straightforward task because the tumor cells resemble those that compose the normal myometrium. However, smooth muscle cells can come to resemble epithelial cells (epithelioid smooth muscle tumors) or endometrial stromal cells or, in the case of sarcoma, become so undifferentiated that smooth muscle differentiation is not apparent on hematoxylin and eosin sections (8, 9). In the first circumstance, the blending of the epithelioid smooth muscle cells into more obvious areas of smooth muscle differentiation in the tumor, if such areas are present, it is a good indicator that the neoplasm in question is a smooth muscle tumor. EMA keratin, actin, and desmin stains may be helpful, but they must be used with caution because smooth muscle cells can be keratin positive and, now and then, can express an antigen recognized by antibodies against EMA (10). Epithelial cells are not desmin positive, however.

Smooth muscle cells can also come to resemble endometrial stromal cells by losing much of their characteristic eosinophilic, sometimes fibrillary, cytoplasm and developing closely approximated round to oblong nuclei of the type more often seen in the proliferative phase in endometrial stromal cells. The neoplasms that usually cause problems are composed of spindled cells with inconspicuous cytoplasm, insignificant cytologic atypia, and absent or rare mitotic figures (Fig. 1). The problem is even more acute when the tumor has infiltrating margins and/or intravascular growth. When the tumor cells are bland, the major differential diagnostic considerations are leiomyoma, intravascular leiomyomatosis, and, because stromal cells may have a spindled appearance, endometrial stromal sarcoma and stromal nodule. Resolution of this differential diagnostic problem depends on ascertaining the differentiation of the spindled cells that compose the neoplasm. Immunohistochemical techniques would, in principle, offer some hope of separating this group of ambiguously differentiated tumors into "smooth muscle" and "stromal" subsets because uterine smooth muscle tumor cells are likely to express desmin, as well as actin and vimentin, whereas

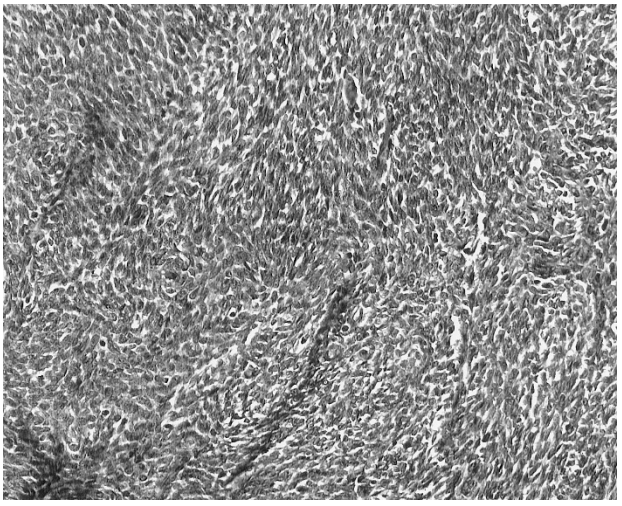

FIGURE 1. This uterine mesenchymal tumor is primarily composed of spindled cells, suggesting a smooth muscle tumor. However, the delicate capillaries, the scant cytoplasm, and the absence of thick-walled vessels favor endometrial stromal differentiation. We consider such tumors to demonstrate ambiguous differentiation and suggest management as for a stromal tumor.

nonmuscle mesenchymal cells more frequently express only actin and vimentin. This seemed to be the case in early studies, but subsequent studies have indicated that there is considerable overlap of stromal and uterine smooth muscle immunophenotypes (11, 12). It is likely that we are dealing with an unresolvable morphologic continuum that represents the neoplastic counterpart of the transitions seen in the normal uterus between stromal differentiation and smooth muscle differentiation; over a certain range of conventional light microscopic appearances, to ask whether a given neoplastic cell is differentiating as a stromal or smooth muscle cell is analogous to asking whether a myofibroblast is truly a smooth muscle cell or a fibroblast: It is neither but has features of both. The differential diagnostic importance of this problem is considerable because the criteria for malignancy are different for smooth muscle tumors and endometrial stromal tumors (mitotic index, atypia, and necrosis for smooth muscle tumors *versus* myometrial infiltration and vascular invasion for stromal tumors).

Features that favor smooth muscle differentiation include large, thick-walled arteries throughout the tumor, desmin-positive tumor cells, fascicular arrangement of the tumor cells, and cleft-like spaces (13). Features that favor endometrial stromal differentiation are plexiform arborizing thin-walled blood vessels, haphazard arrangement of tumor cells, foam cells, and desmin-negative tumor cells. We think desmin staining should be strong and diffuse before it is used as a criterion for smooth muscle differentiation. Smooth muscle cells are occasionally keratin positive.

The sex cord–like elements in the rare uterine tumor resembling ovarian sex cord tumors, a neo-

plasm we classify with the stromal tumors, are very frequently inhibin positive (14). When there is doubt about whether a bland tumor is a leiomyoma or a low-grade stromal sarcoma, we assign the neoplasm to the endometrial stromal group for purposes of treatment and prognosis. To further complicate matters, unequivocal smooth muscle elements may on occasion be present within neoplasms that are otherwise typical endometrial stromal neoplasms, or smooth muscle tumors may feature areas of endometrial stromal differentiation (13). When such mixed neoplasms have infiltrating margins, they tend to behave more like endometrial stromal sarcoma than their smooth muscle counterparts (intravascular leiomyomatosis, leiomyomatosis, or leiomyomas). Conversely, it makes little difference whether a bland tumor is stromal or smooth muscle if infiltration is absent because both stromal nodules and leiomyomas are benign. Intravascular leiomyomatosis is far less common than endometrial stromal sarcoma; we do not think it should be diagnosed unless the tumor cells show unambiguous smooth muscle differentiation.

Definitions of Morphologic Features

Once it is determined that the myometrial tumor in question is in fact demonstrating smooth muscle differentiation, the next step is predicting its clinical behavior. The three morphologic features that we found to be significant predictors of outcome for patients with uterine smooth muscle tumors are cytologic atypia, the level of mitotic index (the mitotic index), and coagulative tumor cell necrosis. These three are used together when evaluating uterine smooth muscle tumors (1). It is important to adhere to the definitions of each of these predictors if results are to be comparable to those we reported in a large series of 215 patients with problematic uterine tumors.

The essential morphologic features (mitotic index, coagulative tumor cell necrosis, and atypia) needed to differentiate the usual leiomyoma from leiomyosarcoma of the uterine corpus do not seem to be significantly altered by treatment with gonadotropin-releasing hormone agonists.

Atypia

Many studies have demonstrated a relationship between cytologic atypia and outcome for uterine smooth muscle tumors (1, 15–17). The problem, as always, is defining significant atypia in a way that is reproducible and easily communicated to others. We found that a two-tiered scheme of absent to mild (insignificant) atypia and moderate to severe (significant) atypia is reasonably reproducible. The assignment of the degree of atypia is based on an assessment of nuclear pleomorphism, nuclear size, nuclear membrane irregularities, chromatin density, and the size and prominence of nucleoli. Significant pleomorphism almost always can be detected at low magnification (×60 to 150) (Figs. 2 and 3). It is rare for tumor cells to manifest enough chromatin and nuclear membrane abnormalities to be considered significantly atypical only at high magnification. Tumors without atypia are composed of smooth muscle cells with uniform nuclei that may be enlarged but that have smooth nuclear contours and evenly distributed chromatin. Mildly (insignificantly) atypical cells show minimal variation in nuclear size and shape, and nucleoli are small.

Tumors with moderate (significant) atypia feature easily found cells with nuclei that are large, plump, and irregular with coarse chromatin. Having more than one or two enlarged abnormal mitotic figures serves to place the tumor in at least the moderately atypical group. Tumors with severe (significant) atypia are obviously pleomorphic and composed of numerous cells with enlarged bizarre nuclei with dense chromatin. Giant cells, often multinucleated, are common in this group, and enlarged and sometimes atypical nucleoli are a common finding. Most common, moderate to severe atypia is diffuse, but it can be focal.

Mitotic index

Mitotic index is based on the number of mitotic figures per 10 hpf. Only definite mitotic figures are counted. Our criteria for accepting mitotic figures are presented in Table 1. Compulsive mitotic counting is not always necessary, depending on the presence or absence of significant atypia and tumor cell necrosis.

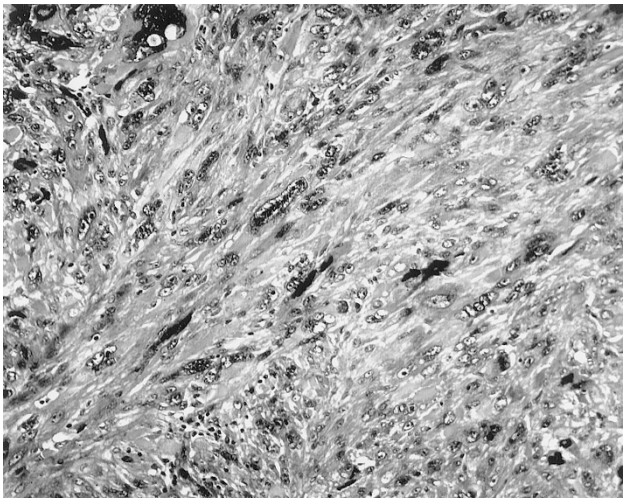

FIGURE 2. Uterine smooth muscle tumor with marked atypia based on the degree of nuclear pleomorphism detected at 60 to 150 × magnification.

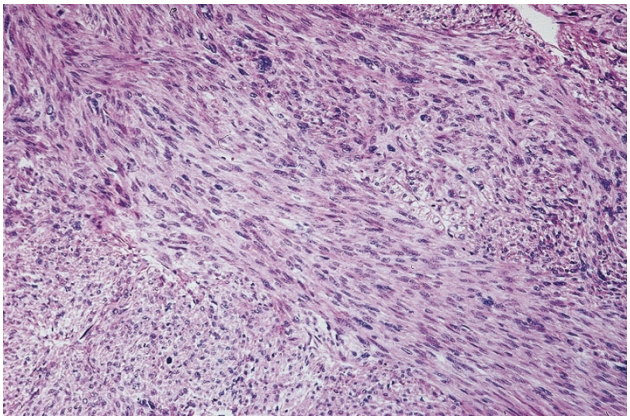

FIGURE 3. Uterine smooth muscle tumor with moderate atypia. The scattered pleomorphic nuclei can be seen even at this low magnification.

TABLE 1. Criteria for Mitotic Figures

1. Hairy extensions of chromatin (condensed chromosomes) must be present, extending from a central clot-like dense mass of chromosomes. The clots may be single (metaphase) or separate (telophase). Hairy extensions from an empty center favor a nonmitosis.
2. The nuclear membrane must be absent, but the cytoplasm is often discernible.
3. Differential diagnosis: lymphocytes, mast cells, stripped nuclei, degenerated cells, precipitated hematoxylin.

Necrosis

In our experience, the presence or absence of necrosis and the type of necrosis are powerful predictors of outcome for patients with uterine smooth muscle tumors (1). We distinguish two types of necrosis in uterine smooth muscle tumors: coagulative tumor cell necrosis and hyalinizing necrosis. Coagulative tumor cell necrosis features an abrupt transition between necrotic cells and preserved cells (Fig. 4). The ghost outlines of the nuclei of the necrotic cells can often be seen throughout the necrotic area, and inflammatory cells are uncommon. This pattern of necrosis is common in clinically malignant smooth muscle tumors and should never be ignored. In contrast, hyalinizing necrosis features a zone of hyalinized collagen interposed between the dead cells and the preserved cells, a pattern reminiscent of an infarcted region being organized by granulation tissue (Fig. 5). Eosinophilic collagen matrix is common in contrast to the necrotic debris seen in tumor cell necrosis, and if dead nuclei can be discerned in areas of hyalinization, the nuclei are uniform and the chromatin is often faint in comparison to the nuclear hyperchromasia and pleomorphism usually visible in tumor cell necrosis. Hyalinizing necrosis is common in leiomyomas and is not helpful in predicting the malignant potential of a smooth muscle tumor. Necrosis secondary to ulceration in submucous leiomyomas features acute inflammatory cells and a peripheral reparative process, whereas ghost outlines of nuclei are usually inconspicuous or absent. This must be distinguished from the coagulative tumor cell necrosis, described previously, that is present in many leiomyosarcomas. Apoplectic leiomyomas are characterized by areas of hemorrhage, but necrosis is absent.

Use of Morphologic Predictors to Classify Uterine Smooth Muscle Tumors

Stratification of uterine smooth muscle tumors with standard (*i.e.*, spindled) smooth muscle differentiation with respect to these three features (atypia, mitotic index, and the presence or absence of coagulative tumor cell necrosis) results in the following five diagnostic categories: (1) leiomyoma, (2) mitotically active leiomyoma (a leiomyoma with more than 10 mf/10 hpf), (3) atypical leiomyoma, (4) leiomyosarcoma, and (5) smooth muscle tumor of uncertain malignant potential (STUMP) (Table 2). The nonstandard subtypes of uterine smooth

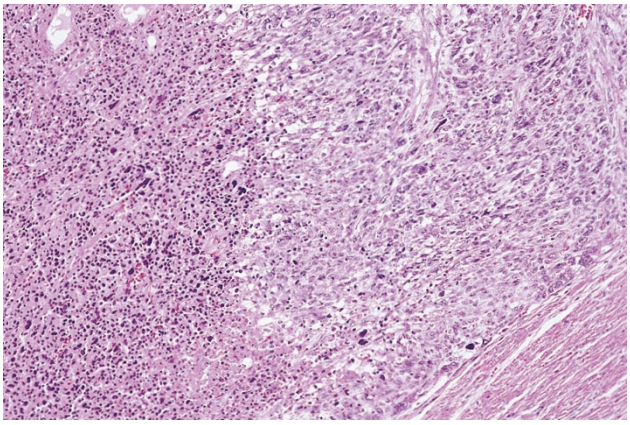

FIGURE 4. Coagulative tumor cell necrosis in leiomyosarcoma. Note the abrupt change from viable tumor on the right to necrotic tumor on the left. The hyperchromatic necrotic tumor cell nuclei on the left are characteristic of those in tumor cell necrosis.

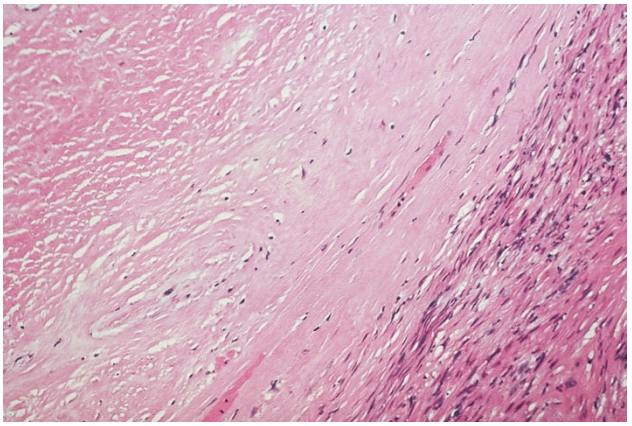

FIGURE 5. Hyaline necrosis in a leiomyoma. Unlike coagulative tumor cell necrosis, there is an eosinophilic band of hyaline between the viable cells at the lower left and the necrotic cells on the right.

TABLE 2. Classification of Uterine Smooth Muscle Tumors with Standard Differentiation[a]

- Leiomyoma
- Mitotically active leiomyoma (≥10 mf/10 hpf)
- Atypical leiomyoma
- Leiomyosarcoma
- Smooth muscle tumor of uncertain malignant potential

[a] Standard differentiation is defined as a tumor composed of spindled muscle cells without a myxoid stroma.

muscle tumors, such as the epithelioid and myxoid type, described below, may be stratified differently with respect to these features, so recognizing nonstandard smooth muscle differentiation is important.

Leiomyoma and Mitotically Active Leiomyoma

Leiomyomas lack coagulative tumor cell necrosis and significant atypia but may have any mitotic index (1, 4–6). If the histologic appearance is that of the usual leiomyoma with neither coagulative tumor cell necrosis nor significant atypia (as defined previously), then nothing clinically useful is gained from determining the mitotic index. The recent literature and our experience indicate that for practical diagnostic purposes, neoplasms without these two features behave in a benign fashion even if the mitotic index is up to 20 mf/10 hpf. Although the reported experience with bland smooth muscle neoplasms without coagulative tumor cell necrosis and with mitotic indices ranging from 5 to 20 mf/10 hpf is limited to approximately 200 patients, this is a substantial experience; accordingly, we think that it is appropriate to label these neoplasms as leiomyomas, and, if desired, the phrase "with increased mitotic index" can be added, although it has no clinical implications. The mitotic figures should be small and normal with no more than one to two abnormal forms in a well-sampled tumor. The same benign behavior is to be anticipated for otherwise characteristic leiomyomas that exhibit hyaline necrosis.

Submucous leiomyomas with surface necrosis may also contain an increased number of cells in division near the necrosis. Granulation tissue-like zones in evolving foci and hyaline necrosis may also feature locally high mitotic indices. Even higher mitotic counts can be found in some but not all leiomyomas removed from women receiving progestogens. Thus, there seem to be several reasons for an increased mitotic index.

Atypical Leiomyoma

The term *atypical* (symplastic leiomyoma) denotes smooth muscle tumors that contain cells that meet the criteria of moderate to severe cytologic atypia defined previously but tumor cell necrosis is absent and the mitotic index is fewer than 10 mf/10 hpf (1, 7) (Fig. 6). Most often, when moderate to severe atypia is present, large cells with pleomorphic hyperchromatic nuclei can be seen at low magnification. If moderate to severe atypia but not tumor cell necrosis is present, the mitotic count serves to stratify the cases into two groups: atypical leiomyomas with a mitotic index of fewer than 10 mf/10 hpf (1 of 46 failed in our group) and leiomyosarcoma with a mitotic index of 10 mf or more per 10 hpf (4 of 10 failed in our group). Obviously, care must be taken for tumors with diffuse moderate to severe atypia without coagulative tumor cell necrosis whose mitotic counts are close to but not quite at 10 mf/10 hpf. Search for abnormal division figures and infiltration is useful in this circumstance because these two features strengthen the presumption that the tumor is leiomyosarcoma. Even if these are not found, some comment in the pathology report about the borderline nature of the tumor is appropriate (see section "Current Uses of STUMP").

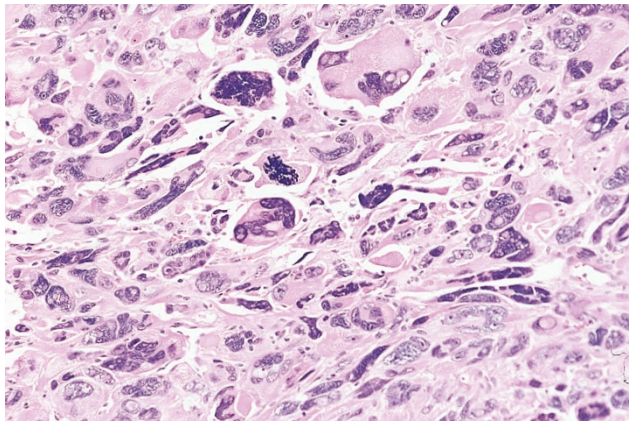

FIGURE 6. Atypical leiomyoma. Although pleomorphism is marked, there is no necrosis. Definite mitotic figures are not found, although there is difficulty in distinguishing mitotic figures from degenerating nuclei.

Leiomyosarcoma

The macroscopic appearance of almost all leiomyosarcomas deviates from the white whorled cut surface pattern that is so characteristic of leiomyomas, although not all grossly peculiar smooth muscle tumors turn out to be leiomyosarcoma. Consequently, all uterine tumors that have deviant gross appearances should be sampled. Leiomyosarcomas are most often hemorrhagic and soft, and many feature the celebrated fish flesh texture. The usual leiomyosarcoma more often than not is more than 5 cm in diameter (15, 16). Microscopically, it is easily recognized as malignant in the vast majority of cases, and usually there is no difficulty in identifying it as a smooth muscle neoplasm. It is common for pleomorphism to be marked, mitotic counts to be in the range of 15 to 30 mf/10 hpf,

and abnormal division figures to be abundant (15–17). In addition, most leiomyosarcomas contain areas of coagulative tumor cell necrosis; in fact, tumors that contain areas of coagulative tumor cell necrosis behave aggressively often enough to be considered leiomyosarcoma if significant atypia is present or tumors of uncertain malignant potential if atypia is absent (1).

Leiomyosarcomas with coagulative tumor cell necrosis almost always have other features associated with malignancy, such as moderate to marked atypia and increased mitotic activity. These signs should be sought to confirm the diagnosis. There is a small set of leiomyosarcomas that are clearly composed of smooth muscle cells but are difficult to distinguish from atypical leiomyoma because the cells are moderately to severely atypical and tumor cell necrosis is not apparent. As noted previously, the mitotic index is used to stratify such tumors into benign and malignant categories. There is another small set of poorly differentiated leiomyosarcomas that are anaplastic with only rare tumor cells demonstrating smooth muscle differentiation.

Current Uses of STUMP

After all is said and done, there exists a very small group of smooth muscle neoplasms of the uterus for which the designation "uncertain malignant potential" is still warranted, at least until additional experience is accumulated and a better estimate of the potential clinical behavior for these lesions can be obtained. We use this term when uncertainty about the evaluation of one or more of the histologic features used to assign cases to the "benign," "atypical," or "malignant" groups is such that we really haven't a clue what to expect from the neoplasm. Examples include minimally atypical smooth muscle neoplasms with a low mitotic index but over which there is uncertainty about the histologic type (*i.e.*, standard *versus* myxoid or standard *versus* epithelioid), the combination of standard smooth muscle differentiation, marked diffuse severe atypia, low mitotic index and uncertainty about whether coagulative tumor cell necrosis is present, and moderate to severe atypia in the face of uncertain mitotic index because possible mitotic figures may be degenerating nuclei mimicking mitotic figures.

Summary of Our Approach to the Evaluation of a Uterine Smooth Muscle Tumor

The steps we take to evaluate any uterine smooth muscle tumor are as follows (Table 3). At low magnification (10× objective), we evaluate the tumor for atypia and tumor cell necrosis. Significant atypia in the form of pleomorphism and tumor cell necrosis almost always can be appreciated at this magnification. If atypia is absent or is at most mild and tumor cell necrosis is absent, then the tumor is a leiomyoma. There is no need to compulsively count mitotic figures if atypia and coagulative tumor cell necrosis are clearly absent. Conversely, if moderate or severe atypia is present without tumor cell necrosis, the tumor is stratified according to the mitotic index as follows. If there are fewer than 10 mf/10 hpf, then it is an atypical leiomyoma; if there are more than 10 mf/10 hpf, then it is leiomyosarcoma. As noted previously, care must be taken when the mitotic index in an atypical uterine smooth muscle tumor approaches but does not reach 10 mf/10 hpf. If both significant atypia and tumor cell necrosis are present, then the neoplasm is leiomyosarcoma regardless of the mitotic index.

TABLE 3. Diagnostic Strategy for Evaluation of Uterine Smooth Muscle Tumors with Standard Differentiation

1. If *atypia* is only *none* or *mild* and *tumor cell necrosis* is *absent,* then the tumor is a leiomyoma. There is no need to compulsively count mitotic figures. If *moderate* to *severe atypia* is present, without tumor cell necrosis, stratification is based on the mitotic index as follows:
   - *Less* than 10 mf/10 hpf: the tumor is an atypical leiomyoma (see text).
   - *Greater* than 10 mf/10 hpf: the tumor is a leiomyosarcoma.
2. If *both moderate to severe atypia* and *tumor cell necrosis* are present, the tumor is a leiomyosarcoma whatever the mitotic index.

Problems that May Be Encountered in the Evaluation of Uterine Smooth Muscle Tumors

Necrosis patterns

The distinction between coagulative tumor cell necrosis and hyaline necrosis is usually straightforward, but problems arise when (1) hyaline is focal and one cannot be sure that the small amount of eosinophilic material present is truly hyaline, (2) the nuclei in the areas of necrosis retain a basophilic appearance and are pleomorphic yet there seems to be hyaline around the necrotic areas, (3) unequivocal individual cell necrosis without hyaline or coagulative tumor cell necrosis is present in an otherwise banal leiomyoma, or (4) mixtures of hyaline and coagulative tumor cell necrosis are present in an otherwise banal leiomyoma or atypical leiomyoma. In all four of these settings, in the absence of any other feature to suggest malignancy, a diagnosis of "uncertain malignant potential" is warranted.

Mitotic figures versus *degenerating nuclei*

In the absence of necrosis, the distinction between "atypical leiomyoma" and "leiomyosarcoma" is based on an assessment of mitotic index. Problems arise when bizarre, smudged, or multilobed nuclei (simulating abnormal mitotic figures) occur in the setting of diffuse severe atypia. We

count only well-formed, "viable" appearing mitotic figures in this setting. The criteria we use for mitotic figures are presented in Table 1. Obviously, a careful search for coagulative tumor cell necrosis is essential in this setting because any degree of such necrosis makes a diagnosis of leiomyosarcoma mandatory.

Scattered markedly atypical cells

In our experience, uterine smooth muscle neoplasms featuring widespread scattered foci of severely atypical cells in the absence of coagulative tumor cell necrosis are clinically benign regardless of the mitotic index. In some cases, the scattered foci are uncomfortably close together; at what point does this proximity warrant classification as leiomyosarcoma if the mitotic index is 10 mf or more per 10 hpf? Because of the rarity of cases of this sort, any quantitative guideline would be completely arbitrary. Our current convention for areas of atypia to be considered focal is as follows: The atypical foci should be separated by at least one 4× objective field (15× ocular) of nonatypical smooth muscle fascicles.

Other observations that may be useful

Although infiltration did not prove to be an independent predictor in the multivariate analysis of our 213 cases, almost all leiomyosarcomas infiltrate, as may some leiomyomas (1). However, when a problematic smooth muscle tumor has infiltrating margins, great care should be taken because the benignancy of such a lesion cannot be ensured, and most often a designation of uncertain potential is warranted. Likewise, having more than just one or two abnormal mitotic figures is a feature much more common in leiomyosarcoma than in leiomyoma. Although atypia of the type found in leiomyosarcoma is almost always apparent at 10× magnification, there are rare leiomyosarcomas in which the tumor cells are enlarged but relatively uniform and have marked chromatin abnormalities. Before labeling a smooth muscle tumor as a leiomyoma, it is always wise to look at the nuclei in several areas at higher magnification to be sure there are not significant chromatin abnormalities. Cells that compose leiomyomas are often enlarged and often vesicular, but they do not have marked chromatin abnormalities or significantly irregular nuclear outlines.

Subtypes of Uterine Smooth Muscle Tumors

The rules described previously for predicting the behavior of uterine smooth muscle tumors are for tumors that feature standard differentiation (*i.e.*, the tumor is composed of spindled smooth muscle cells). When the smooth muscle tumor is composed of epithelioid smooth muscle cells in more than just a few areas or the tumor has a myxoid stroma, the rules must be altered as described next. Several unusual types of uterine smooth muscle tumors are also described (Table 4).

Epithelioid smooth muscle tumors

Smooth muscle cells can become rounded to the point that they resemble epithelium; when this occurs, they are designated as epithelioid (8, 9) (Fig. 7). Such differentiation in more than just a few foci of a uterine smooth muscle tumor is an ominous finding because the absence of cytologic atypia and necrosis is no guarantee of a clinically benign course when the tumor contains more than 5 mf/10 hpf. All epithelioid uterine smooth muscle tumors with tumor cell necrosis in our unpublished series behaved in a malignant fashion. Conversely, all seven epithelioid tumors with a mitotic index of less than 5, at most, with minimal cytologic atypia, and without coagulative tumor cell necrosis behaved benignly. The experience with epithelioid uterine smooth muscle tumors as a group is limited even when all of the literature is considered. Indeed, tumors with moderate to severe atypia without necrosis at a mitotic index of less than 5 should be classified as of uncertain malignant potential because our experience is too limited to be certain about their aggressive potential.

Care should be taken in interpreting uterine smooth muscle cells as epithelioid. The usual elongate smooth muscle cell when cut in cross-section can appear round, and the observer should be sure that round cells in question have abundant cytoplasm and they do not represent cross-sectional diameters of elongate cells.

Myxoid smooth muscle tumors

Many uterine smooth muscle tumors that exhibit gross evidence of cystic change or myxoid stroma feature on microscopic evaluation islands of bland and often collagenized smooth muscle cells set in areas of edematous connective tissue. Large blood vessels are characteristically suspended in these myxoid areas. Such changes are characteristic of leiomyomas (18). Conversely, myxoid differentia-

TABLE 4. Subtypes of Uterine Smooth Muscle Tumors

Nonstandard differentiation
Epithelioid
Myxoid
Benign metastasizing leiomyoma
"Parasitic" leiomyoma
Unusual histologic patterns found in leiomyomas
Lipoleiomyoma
Neurilemmoma-like
Leiomyomatosis (infiltrating leiomyoma)
Plexiform tumorlet
Diffuse perinodular and other patterns of hydropic degeneration (18).

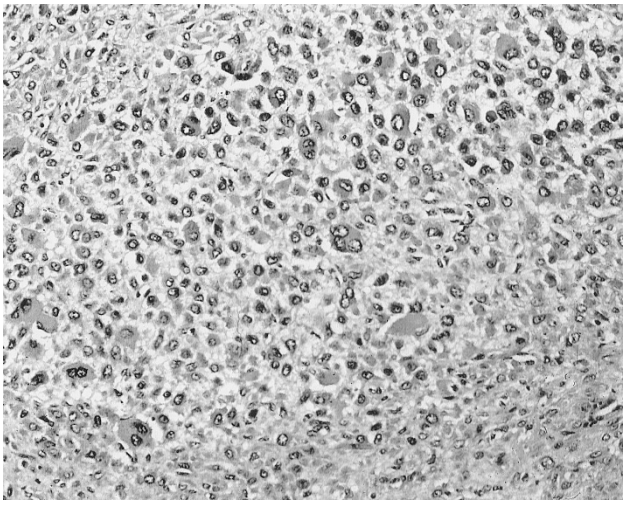

FIGURE 7. Epithelioid smooth muscle tumor. The constituent cells are round with abundant cytoplasm.

tion coupled with enlarged and atypical cells is an ominous finding; four of seven such uterine tumors failed in our series. The degree of atypia resembles that found in the less cellular examples of myxoid myxofibrosarcoma. Our diagnostic terminology is as follows: Benign tumors are considered to be leiomyomas with myxoid stroma. In this circumstance, the cells are small and uniform and there is no atypia or at most mild atypia, the mitotic index is less than 5 mg/10 hpf, and there is no infiltration. Malignant tumors are myxoid leiomyosarcomas. These tumors feature moderate to marked atypia with or without necrosis and any mitotic index, and the margins are usually infiltrating (19). In other words, for myxoid smooth muscle tumor, paucity or absence of mitotic figures is no assurance of benignancy.

Benign metastasizing leiomyoma

On very rare occasions, women with a mitotically inactive, cytologically bland, non-necrotic uterine smooth muscle tumor may develop similarly morphologically benign extrauterine smooth muscle deposits (usually in the lymph nodes or in the lungs) in the absence of a primary smooth muscle malignancy in the gastrointestinal tract, retroperitoneum, or other nonuterine site. Because one explanation for this phenomenon is the spread of histologically benign smooth muscle from the uterine leiomyoma to distant sites, this process has been labeled "benign metastasizing leiomyoma." The criteria for this very unusual diagnosis are understandably strict, and an absolute minimal guideline is that all smooth muscle tumors must have been thoroughly examined histologically and judged to be unquestionably benign morphologically. The implication of this diagnosis is that on very rare occasions, morphologic features are noninformative about the potential for a uterine smooth muscle tumor to metastasize. This approach eliminates labeling these bland metastasizing tumors as leiomyosarcoma for eminently sensible reasons: Thousands of clinically benign smooth muscle tumors would have to be labeled malignant to anticipate the extremely rare clinically malignant tumor in this morphologic range. The metastatic bland smooth muscle deposits develop most often in lymph nodes or the lung; in rare instances, the benign smooth muscle deposits are found initially in abdominal lymph nodes and subsequently in the lungs. The pulmonary nodules usually progress slowly, sometimes to the point of producing pulmonary insufficiency, and they may respond to hormonal treatment. Because a few women with benign pulmonary smooth muscle tumors have not had uterine tumors, some investigators believe that the pulmonary process is unrelated to the presence of uterine smooth muscle tumors; instead, they consider the lung nodules to be separate from the uterine smooth muscle proliferations.

Parasitic leiomyoma

The older literature suggests that leiomyomas may detach themselves from an initial subserosal location and attach to some other pelvic structure or even grow in the retroperitoneum. This improbable event presumably takes place through the mediation of a combination of infarction and inflammatory adhesions. We have never seen such a lesion. A diagnosis of parasitic leiomyoma should be made with great caution because smooth muscle neoplasms that arise in the retroperitoneum and gastrointestinal tract and that have recurring or metastatic potential are notorious for being morphologically bland and having few or no mitotic figures.

Intravascular growth

Morphologically benign uterine smooth muscle tumors may be associated with intravascular growth, and, on occasion, leiomyosarcoma will invade blood vessels. When the smooth muscle is morphologically benign, three situations are distinguished: solitary otherwise unremarkable leiomyoma associated with a microscopic focus of intravascular neoplasm within the confines of the leiomyoma, grossly visible wormlike intravascular masses of cytologically benign smooth muscle, or microscopic intrusions of benign smooth muscle into vessels outside the confines of an otherwise unremarkable leiomyoma (20). The first of these is designated leiomyoma with vascular intrusion, and this is benign without implication of recurrence. The latter two are designated intravascular leiomyomatosis because such lesions recur in vessels outside the uterus and sometimes in vessels outside the pelvis. The definition of intravascular leiomyomatosis requires any extrauterine benign smooth muscle

to remain within vascular lumens or within the chambers of the heart. The presence of morphologically benign smooth muscle within parenchymal organs excludes intravascular leiomyomatosis and raises the possibility of benign metastasizing leiomyoma or low-grade leiomyosarcoma.

It is of course very important to distinguish intravascular leiomyomatosis from leiomyosarcoma with vascular invasion (21). A mitotic index above 5 mf/10 hpf is distinctly unusual in intravascular leiomyomatosis, and tumor cell necrosis is not allowed. The term *uncertain malignant potential* is appropriate for cases with bland histologic features but with a mitotic index of 5 to 15 mf/10 hpf. Moderate to marked atypia and a mitotic index of more than 5 in an intravascular smooth muscle tumor is indicative of leiomyosarcoma.

Another lesion, which not infrequently features vascular invasion, is low-grade endometrial stromal sarcoma. Distinguishing this from intravascular leiomyomatosis amounts to discriminating endometrial stromal differentiation from smooth muscle differentiation. In most cases, this is not difficult, but, as noted previously, differentiation in some cases is ambiguous. We assign cases with ambiguous differentiation to the category of low-grade endometrial stromal sarcoma.

Unusual histologic patterns found in leiomyomas

It is not an uncommon experience to encounter a uterine smooth muscle tumor that is not obviously malignant using the features described above but that has very unusual histologic patterns. Through the years, these have been categorized and given labels. The most commonly recognized histologic patterns are presented in Table 4. Details about the morphologic features of these unusual variants of leiomyoma can be found in standard texts and in Clement *et al.* (18).

ENDOMETRIAL STROMAL NEOPLASMS

Endometrial stromal neoplasms are composed of cells with inconspicuous cytoplasm and round to oblong nuclei that, in the usual case, are light-microscopically ultrastructurally and immunohistochemically identical to the endometrial stromal cells found in proliferative endometria (22–25). Characteristically, this monotonous proliferation of cells is interrupted by a regular network of delicate ramifying small vessels resembling spiral arteries and capillaries (Fig. 8). Stainable glycogen and mucin are absent. It is vital that this definition of neoplastic stromal differentiation be followed because major patient outcome studies are based on it and only minor deviations from it are allowed. Occasionally, an endometrial stromal neoplasm

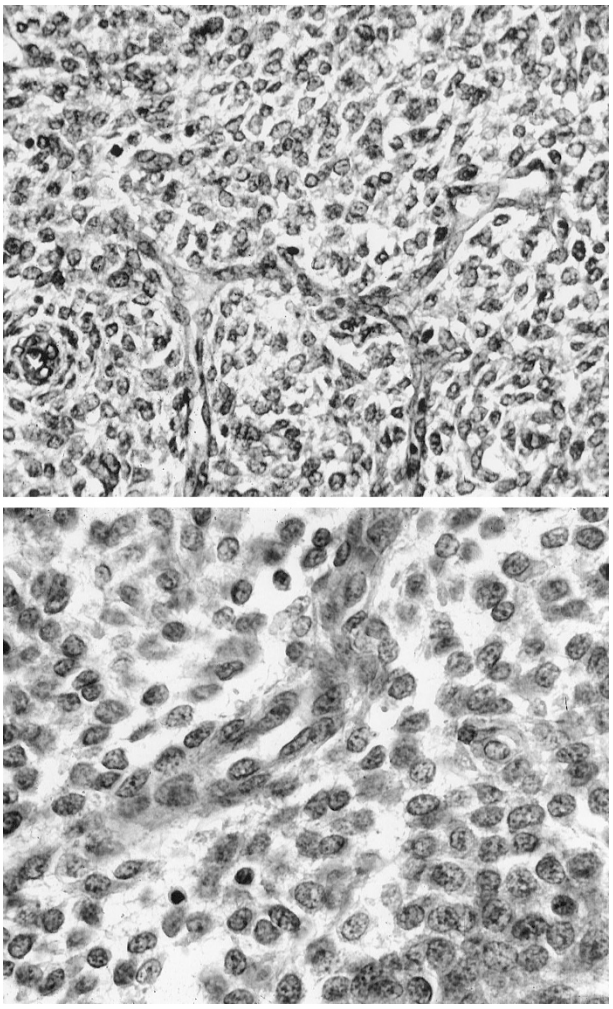

FIGURE 8. **A** and **B**, low- and high-power views of the cells that compose endometrial stromal sarcoma. Note the resemblance to proliferative phase endometrial stroma. The arching thin-walled capillaries are characteristic of a stromal neoplasm.

contains an abundance of distinctive hyalinized osteoid-like collagen, and in some cases collagenization is so extensive as to reduce the cellular component to attenuated chains of cells, resulting in a picture reminiscent of a hyalinized leiomyoma. This pattern of hyalinization may be preserved in pelvic recurrences and pulmonary metastases. Foam cells may be present in stromal neoplasms and are morphologically identical to the foam cells seen in endometrial hyperplasia and carcinoma.

Endometrial stromal neoplasms are divided into two classes, stromal nodule and stromal sarcoma, based on the presence of infiltrating margins or vascular intrusion in the latter and circumscribed margins in the former (24, 26). Other than infiltration and vascular intrusion, the two lesions are indistinguishable histologically. Determining whether infiltration of the myometrium is present is not always a straightforward task. Often there is a subtle interdigitation of stromal and smooth muscle cells when a compressive margin is examined at high magnification. We do not

count this as an infiltrative margin. The pattern we require for infiltration is irregular, jagged islands or tongues of neoplastic stromal cells present between smooth muscle bundles of the surrounding normal myometrium (25). For vascular involvement, clumps of tumor cells must be present in spaces within the myometrium.

Current taxonomic practice allows for endometrial stromal neoplasms to produce benign glandular elements (27) (Fig. 9). When glands are numerous, the possibility of adenosarcoma should be entertained. Neoplasms with focal sex cord–like arrangements of epithelioid cells in cords, tubular structures, trabeculae, or sheets are also assigned by us to the stromal group, although their taxonomic status is less secure; they may be more closely related to smooth muscle neoplasms. Immunohistochemical studies have supported the close relationship of these lesions to ovarian sex cord tumors because the uterine sex cord–like tumors not infrequently express ovarian sex cord stromal markers recognized by inhibin and on occasion may be keratin positive (14).

Clinicopathologic Correlation

Endometrial stromal nodules are benign. Traditionally, endometrial stromal sarcomas have been stratified on the basis of the mitotic index into a low-grade group (<10 mf/10 hpf) and a high-grade group (>10 mf/10 hpf) because of perceived differences in outcome (24). Evans challenged this concept. He held that what had been traditionally regarded as one disease (endometrial stromal sarcoma) is in some sense two diseases: one that behaves like a low-grade malignant neoplasm and resembles (in terms of its differentiated features) normal proliferative phase endometrial stroma and another that behaves clinically like a high-grade sarcoma and is composed of cells that are larger and more pleomorphic than is allowed in the definition of stromal sarcoma (23). In our review of more than 100 endometrial stromal sarcomas selected on the basis of Evans's definition, we found that 45% of Stage I patients who had both rare mitotic figures and minimal atypia had one or more relapses, and of these, two (13%) died of disease at 85 months and 30 years, respectively (22). There was no significant difference in relapse rate or survival between patients on either side of the 10 mf/10 hpf line as long as the constituent cells resembled proliferative phase endometrial stromal cells. Patients with high-stage disease fared significantly worse than those with disease confined to the uterus; high-stage patients tended to have higher mitotic indices, and within the high-stage group, patients with a mitotic index of 10 mf or more/10 hpf fared worse than those with a mitotic index of less than 10. Thus, the single most important prognostic factor seems to be the stage at presentation.

Again, bland histology and low mitotic indices are no guarantees that recurrence will not occur. The size of the uterine primary in Stage I patients is poorly correlated with clinical outcome; endometrial stromal sarcomas measuring less than 4 cm may recur.

Therefore, once the surgical stage is known, mitotic index provides no further predictive information for Stage I patients but does seem to provide additional information about outcome in high-stage patients. These findings greatly diminish the usefulness of the mitotic index as a predictor. Accordingly, we no longer use the high grade/low grade distinction advocated by Norris and Taylor, although we append the label "low grade" to all endometrial stromal sarcomas in our diagnosis line to indicate that as uterine sarcomas go, endometrial stromal sarcomas are relatively low grade (22, 24).

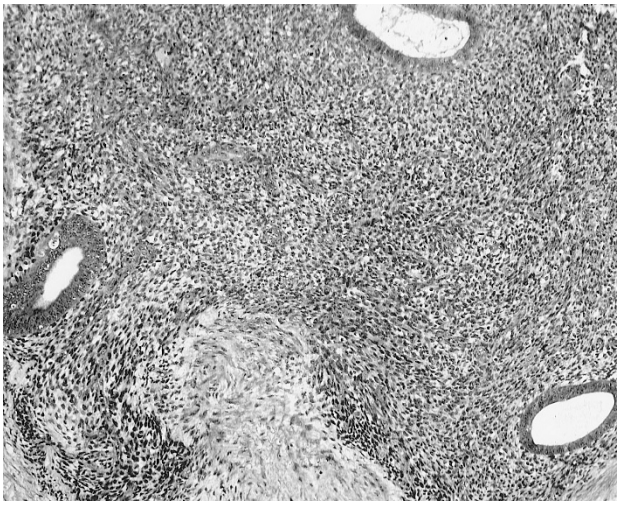

FIGURE 9. Low-grade endometrial stromal sarcoma with glands. The glands are small and are not surrounded by a cuff of hypercellular stroma as would be expected in adenosarcoma.

Endometrial stromal tumors in curetting and biopsies

When fragments of proliferative phase endometrial stroma without glands are present in curetting specimens, the possibility of an endometrial stromal tumor should be considered. Imaging studies may help support the diagnosis by demonstrating a mass lesion. Because the distinction between stromal nodule and low-grade stromal sarcoma is based on whether infiltration is present, a diagnosis of stromal sarcoma is rarely possible on the basis of a curetting or biopsy specimen. For women for whom uterine conservation is not an issue, hysterectomy will be diagnostic. For women who desire uterine preservation, a combination of imaging studies and hysteroscopy is warranted.

Differential Diagnosis

Endometrial stromal neoplasm versus *smooth muscle tumor*

When a problematic uterine tumor is composed of uniform cells that could be either smooth muscle or endometrial stromal but has circumscribed margins, the distinction between smooth muscle and endometrial stromal tumors is clinically unimportant because both leiomyoma and endometrial stromal nodules are benign. Conversely, if the margins are infiltrating, then the tumor may be either a leiomyoma or a low-grade endometrial stromal sarcoma, a distinction of obvious importance. Our strategy in this situation has been presented in the section "Determining the Direction of Differentiation" near the beginning of this article. If the direction of differentiation remains ambiguous, we assign the tumor to the low-grade stromal category, particularly if the infiltration takes the form of tongue-like islands of tumor cells within the myometrium or vascular invasion is present. Unequivocal smooth muscle elements may be present within neoplasms that are otherwise typical endometrial stromal neoplasms; such tumors tend to behave more like stromal sarcoma than their smooth muscle counterparts (intravascular leiomyomatosis, leiomyomatosis, or leiomyomas) (13). Intravascular leiomyomatosis is far less common than endometrial stromal sarcoma; it should not be diagnosed unless the tumor cells show unambiguous smooth muscle differentiation.

Leiomyosarcoma with vascular invasion and undifferentiated uterine sarcoma is distinguished from stromal sarcoma on the basis of its cytologic atypia, which is greater than is allowed in stromal sarcoma, and its lack of plexiform vasculature. In addition, the tumor cells in leiomyosarcoma are often arranged in long fascicles, at least focally. Mitotic indices of more than 10 mf/10 hpf are unusual in stromal sarcoma but do not exclude the diagnosis.

Endometrial stromal sarcoma versus *adenosarcoma*

Low-grade endometrial stromal sarcoma may feature foci of glandular differentiation, raising the differential diagnostic consideration of adenosarcoma because many adenosarcomas have endometrial stromal cells as their mesenchymal component (28). The glands in endometrial stromal sarcoma are usually sparse and small without stromal condensation around them, whereas the glands in adenosarcoma tend to be large and dilated and often feature periglandular stromal condensation (Figs. 9 and 10). However, in the range in which glands become numerous and stromal condensation is questionable, there is considerable overlap between these two lesions when the mesenchymal element is endometrial stromal sarcoma. Fortunately, there is little at stake in this distinction because both endometrial stromal sarcoma with glands and adenosarcoma with a low-grade endometrial stromal proliferation as its mesenchymal component are low-grade neoplasms. It is worth knowing that the prognosis for both adenosarcoma and low-grade stromal sarcoma is worse when the neoplasms are primary in extrauterine sites.

Adenomyosis without glands and intravascular intrusion by benign proliferative phase endometrial stroma

Occasionally, adenomyotic foci may not contain glands, raising the possibility of endometrial stromal sarcoma (27). Both stromal sarcoma and stromal nodule produce mass lesions, and small foci of gland-free endometrial stroma within the myometrium in the absence of a mass are almost always a manifestation of adenomyosis. Looking for the characteristic smooth muscle hypertrophy that accompanies most foci of adenomyosis and searching for gland-containing adenomyosis elsewhere in the myometrium usually establishes the correct diagnosis. Very rarely, fragments of proliferative phase stroma without glands are found in vessels within the myometrium. As long as there is no mass lesion present and as long as the intravascular fragments are microscopic, this phenomenon is harmless and is undoubtedly a manifestation of adenomyosis.

UNDIFFERENTIATED UTERINE SARCOMA

Undifferentiated uterine sarcoma is less common than endometrial stromal sarcoma. Undifferentiated uterine sarcomas are obviously malignant neoplasms and lack "endometrial stromal" features (bland uniform cells with scant cytoplasm associ-

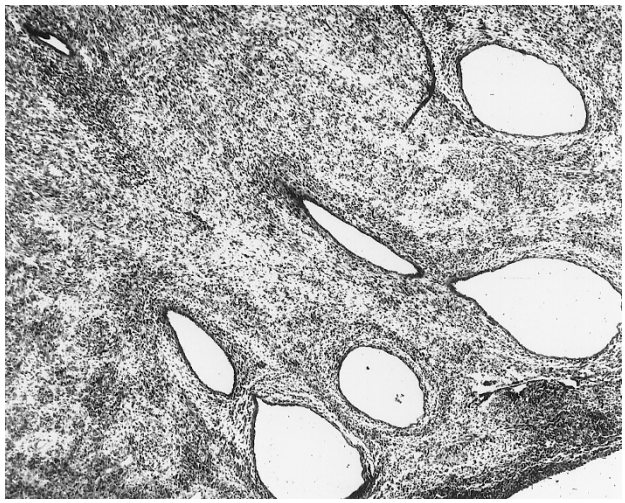

FIGURE 10. Adenosarcoma in which the glands are dilated and surrounded by a cuff of stomal cells.

ated with an arborizing plexiform vasculature) (22, 23). In the usual case, necrotic fleshy tumor fills the uterine cavity, and microscopically the neoplasm features marked nuclear anaplasia, at least some degree of pleomorphism, and mitotic counts in excess of 20 mf/10 hpf. Occasionally, the mitotic index is less than 10 mf/10 hpf. The tumor cells do not demonstrate any recognizable direction of differentiation, but they appear "sarcomatous" and almost always are negative for cytokeratin. A plexiform vascular pattern is absent. Distinguishing endometrial stromal sarcoma from this anaplastic high-grade sarcoma is imperative: the former is a clinically indolent process, whereas the latter is an aggressive malignant neoplasm with a high mortality within 2 years of diagnosis. Undifferentiated uterine sarcoma has sometimes been designated as "high grade" endometrial stromal sarcoma, a nomenclatural practice we think is unwarranted because the cells do not resemble proliferative phase endometrial stromal cells and because the tumor cells usually do not respond to hormonal therapy as do the cells in many low-grade endometrial stromal sarcomas.

MIXED MÜLLERIAN NEOPLASMS

Mixed müllerian neoplasms are composed of both neoplastic epithelium and neoplastic mesenchyme. These tumors exhibit a range of clinical behavior from benign (adenofibroma, adenomyoma, and atypical polypoid adenomyoma) to malignant (adenosarcoma and carcinosarcoma) (29). Classification of this group of tumors is based on an evaluation of both the epithelial and mesenchymal component and results in a 3-fold classification. Adenofibroma, adenomyoma, and atypical polypoid adenomyoma (APA) are neoplasms with both benign epithelium and benign proliferating stroma. Adenosarcomas are composed of benign epithelium and a mitotically active or sarcomatous stroma. Carcinosarcomas, better known as malignant mixed müllerian tumors, feature malignant epithelium and malignant stroma.

Atypical Polypoid Adenomyoma

APA is a biphasic neoplasm whose epithelial component demonstrates complex atypical endometrial hyperplasia and whose mesenchymal component is bland smooth muscle or a mixture of fibrous tissue and smooth muscle (30–32). Although the mesenchymal component of APA is usually smooth muscle, it is our experience that many lesions have a hybrid fibrous and smooth muscle stroma (30). Morular metaplasia is present is more than 90% of the cases and is a useful marker of this lesion (Fig. 11). On occasion, the glands in otherwise characteristic APA have the architectural features of well-differentiated adenocarcinoma. Such lesions can extend into the myometrium, and we label them as APA of low malignant potential (30, 31). Another characteristic feature of all APAs is the patient's age, which generally ranges from 35 to 45. The combination of the patient's youth, the prominent morular metaplasia, the characteristic smooth muscle or hybrid smooth muscle and fibrous stroma, and the focal nature of the process almost always allow recognition of the process.

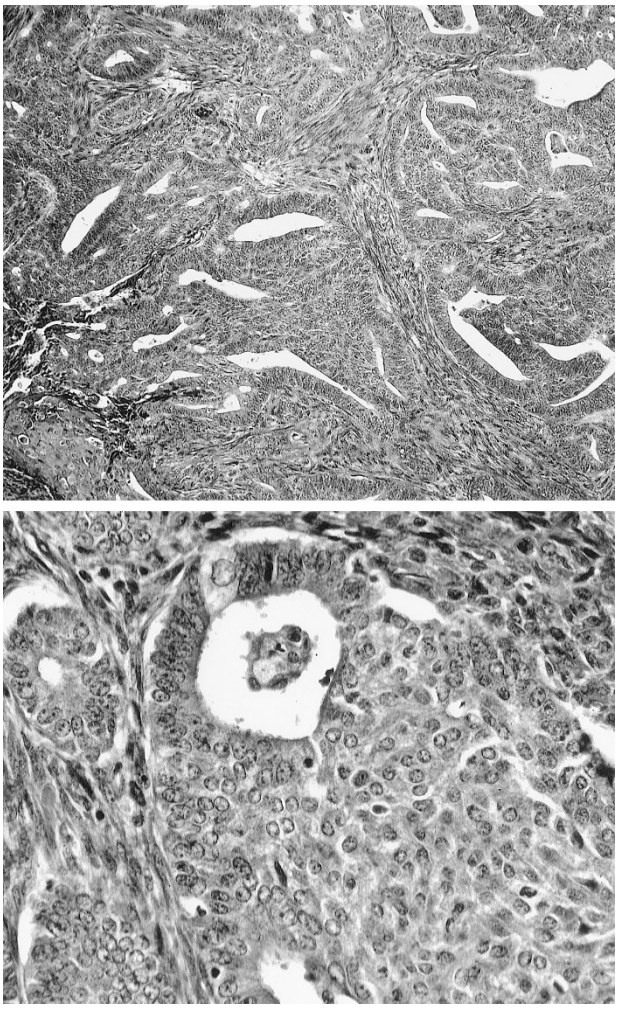

FIGURE 11. **A** and **B**, the characteristic features of atypical polypoid adenomyoma—atypical complex glandular hyperplasia, a smooth muscle stroma, and morules—can be seen in these two photomicrographs.

Clinicopathologic correlation

APA is a persisting or recurring lesion, but it does not metastasize. Most APAs do not invade the myometrium, although APA of low malignant potential on occasion may involve the superficial myometrium. However, no APA has been reported to extend beyond the uterus. Thus, it seems reasonable to consider conservative therapy for patients who want to preserve their uterus. Approximately one

third of patients who had their APA treated with something less than hysterectomy have had successful pregnancies. Because APA may represent an increased risk for developing subsequent carcinoma, patients who are treated conservatively should have long-term follow-up.

Adenofibroma and Adenosarcoma

Adenofibroma and adenosarcoma feature benign glands and a stromal proliferation that varies from mitotically inactive and bland (adenofibroma) to bland stroma that demonstrates more than 2 to 4 mf/10 hpf (low-grade adenosarcoma) to frankly sarcomatous stroma (adenosarcoma) (33–35). Although the distinction between adenofibroma and low-grade adenosarcoma has been set somewhere between 2 and 4 mf/10 hpf, the two lesions typically have other differences (33, 35). Adenofibroma closely resembles its namesake in the ovary and features broad papillary structures containing paucicellular hyalinized fibrous or endometrial stroma. These papillary structures are often envaginated into cystic epithelial lined spaces. Adenosarcoma is more often multicystic and often features a smoother surface, although it can be papillary. Most adenosarcomas are low grade and contain uniformly distributed, often dilated glands scattered throughout a cytologically bland and at least focally cellular stroma that most often resembles endometrial stroma. Commonly, the glands are marked by intraluminal polypoid protrusions and usually the mesenchymal cells condense in a cellular band around the dilated glands, a feature that aids in the identification of adenosarcoma. A minority of cases have either a morphologically malignant mesenchymal component and benign glands or a pure mesenchymal component (overgrowth) in some part of the tumor (conventionally more than 25%) associated with the mixture of benign glands and mitotically active or sarcomatous stroma characteristic of adenosarcoma elsewhere (36). The stroma in areas of stromal overgrowth may be bland or sarcomatous. Heterologous sarcoma is seen in one fourth of adenosarcomas with stromal overgrowth, and among these, rhabdomyosarcoma is particularly common.

Differential diagnosis

Distinguishing adenosarcoma from adenofibroma is accomplished by identifying cellular mesenchyme arranged in a periglandular fashion and by establishing the mitotic index, which, as noted, has been set between 2 and 4 mf/10 hpf for a diagnosis of low-grade adenosarcoma. We consider tumors with bland stroma and borderline mitotic counts to be of uncertain malignant potential, particularly if subepithelial stromal condensation, a marker of adenosarcoma, is present.

In addition to adenofibroma, the differential diagnosis of adenosarcoma includes endometrial stromal sarcoma with glands. The dividing line between these two has never been set, but dilated glands with intraluminal polypoid protrusions and periglandular stromal condensation are features of adenosarcoma, whereas the glands in endometrial stromal sarcoma are usually focal and smaller and are not surrounded by hypercellular stroma. As long as the stroma is as bland as that in low-grade stromal sarcoma, the tumor will behave like low-grade endometrial stromal sarcoma.

Clinicopathologic correlation

Patients with adenofibroma and adenosarcoma are usually postmenopausal, although both can occur in younger women. Most patients with adenosarcoma, particularly low-grade adenosarcoma, are cured by hysterectomy. In the absence of stromal overgrowth, a 15 to 25% recurrence rate is the rule; when stromal overgrowth is present, a recurrence rate of 45 to 70% is expected. Consequently, we label adenosarcoma with bland stroma, with a low mitotic index, and without stromal overgrowth as being of low malignant potential. Patients at most risk for recurrent disease are those who have high-stage tumor at the time of diagnosis, deep myometrial invasion (>30% through the uterine wall), a high-grade sarcomatous component, and tumor with stromal overgrowth.

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

These high-grade malignant neoplasms feature carcinoma and sarcoma and are usually not difficult to diagnose. The usual tumor is composed of obvious carcinoma, which may be mucinous, squamous, endometrioid, high-grade papillary, clear cell, undifferentiated, or mixtures of these types, and a second component of spindle cells, which, when heterologous differentiation or leiomyosarcoma is present, is easy to recognize as sarcomatous (37–40). Difficulties arise primarily in trying to decide whether an undifferentiated component is carcinoma or sarcoma. Unfortunately, keratin stains are not helpful in this circumstance because sarcomatous elements in carcinosarcoma may be composed of keratin-positive cells. This suggests that uterine carcinosarcomas may in fact be metaplastic carcinomas (37, 40).

Carcinosarcomas usually grow as fleshy, necrotic, hemorrhagic masses that often fill the uterine cavity. Cervical, myometrial, and extrauterine involvement at the time of hysterectomy is common. At the microscopic level, both the high-grade nuclear fea-

tures and the biphasic patterns of the neoplasm are apparent in most cases. The epithelial component of carcinosarcoma as noted above may be any type of müllerian carcinoma, but the endometrioid type is the most common. In the past, the stromal components have been divided into homologous types (leiomyosarcoma, stromal sarcoma, and fibrosarcoma) and heterologous types (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, and liposarcoma). However, there are few recent data to suggest that this morphologic division is clinically useful. Conversely, identification of heterologous sarcoma is often diagnostically useful in identifying the tumor as a carcinosarcoma rather than pure carcinoma.

Clinicopathologic correlation

Carcinosarcoma is most often a disease of older postmenopausal women whose clinical course is that of a high-grade aggressive malignant neoplasm. As many as one third of the patients have clinical evidence of extrauterine spread at the time of presentation; in some series, as many as half of the patients thought to have Stage I disease clinically are found to have higher stage disease at surgery. No adjuvant therapy has been shown to be effective in a randomized trial by the Gynecologic Oncology Group, and treatment of persistent or recurrent tumor by chemotherapy or radiation practically never results in cure. There are no consistent differences in survival between patients whose sarcomatous element is homologous or heterologous, but important prognostic features are the stage, size of the tumor, and depth of myometrial invasion. Essentially, the only patients who have long-term survival are those with small tumors that are at most minimally mildly invasive. However, even tumors that seem to be confined to the endometrium or to an endometrial polyp can metastasize. The types of sarcoma, the mitotic index, and the grade of the sarcoma have not been shown to be significantly related to survival (40). There are conflicting reports about the significance of vascular invasion, cervical involvement, and the subtype of carcinoma. The Gynecologic Oncology Group has reported that the subtype (especially serous and clear cell) and grade of the carcinomatous element are significant predictors of survival. Moreover, metastases from almost all carcinosarcomas are composed exclusively of the carcinomatous element (37, 40).

The pathology report of a patient with carcinosarcoma should contain information about the size and location of the tumor, the extent of myometrial invasion, the presence or absence of vascular invasion, the type of carcinoma, and the status of the resection margins as well as the type and location of metastases, if any.

Differential Diagnosis

Adenosarcoma versus *carcinosarcoma*

Adenosarcoma and carcinosarcoma are distinguished by determining whether the epithelial component is benign or malignant. Ambiguous cases are unusual, but when there is uncertainty in a curettage or biopsy specimen, resolution may have to await hysterectomy.

Carcinosarcoma versus *proliferations of malignant undifferentiated cells*

This not uncommon problem revolves around whether undifferentiated or poorly differentiated areas of a malignant neoplasm are carcinoma or sarcoma. In one scenario, unequivocal carcinoma is identified but it is associated with areas of undifferentiated tumor cells that are not definitely sarcoma or carcinoma. Immunohistochemical stains have been advocated in this situation, but some high-grade carcinomas will not react with keratin antibodies and the cells in morphologically unequivocal sarcomatous areas of carcinosarcoma may express keratin. If the uncertainty persists after many sections have been taken from the hysterectomy specimen, it is useful to know that in clinical terms very little depends on distinguishing between carcinosarcoma and high-grade anaplastic carcinoma.

The second situation involves an endometrial sample composed of sheets of undifferentiated malignant cells with neither a discernible carcinomatous component nor a sarcomatous one. Five different entities need to be considered: pure high-grade carcinoma, pure sarcoma, lymphoma or leukemia, carcinosarcoma in which the undifferentiated areas have been sampled, and metastatic carcinoma.

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