Pathology and Pathophysiology of Uterine Smooth-Muscle Tumors

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Smooth-muscle tumors of uterine origin encompass a broad family of neoplasms. The leiomyoma, by far the most common of all the neoplasms, generally is hormone sensitive, with rates of growth semiquantitatively related to estrogen and progesterone receptor levels. Several forms of degenerative change can occur in the leiomyoma. The most common is hyaline degeneration, which is important in that it should not be mistaken for the coagulative tumor cell necrosis seen in leiomyosarcoma. Red degeneration (necrobiosis) is a form of degeneration that occurs characteristically but not exclusively in pregnancy, and the process is often the cause of pain and fever. Several forms of treatment have been used medically in the treatment of leiomyoma. Gonadotropin-releasing hormone analogs or agonists or selective arterial embolization with polyvinyl-formaldehyde particles may lead to substantial degeneration or infarction of the leiomyoma, respectively. Several variants of leiomyoma, the cellular and symplastic leiomyomas, are important to recognize, as they may be misinterpreted as sarcoma. In addition, there are two unusual growth patterns of leiomyoma that are important to recognize. Both the benign metastasizing leiomyoma and disseminated peritoneal leiomyomatosis are found outside the uterus, and neither is malignant. Recent studies offer insights into their origin and hormonal influences. From a diagnostic and therapeutic point of view, the leiomyosarcoma, while rare, is clinically of great import. Coagulative necrosis, cytologic atypia, and mitotic counts are all important in diagnosing the condition. Key words: arterial embolization, benign metastasizing leiomyoma, disseminated peritoneal leiomyomatosis, gonadotropin-releasing hormone analogues or agonists, intravascular leiomyomatosis, leiomyoma, leiomyosarcoma, pathology, peritoneum, smooth-muscle tumors, symplastic leiomyoma, uterus. — Environ Health Perspect 108(suppl 5):779–784 (2000).


The uterine leiomyoma is the most common gynecologic neoplasm in women of reproductive age. Many leiomyomas are small and asymptomatic, but larger leiomyomas or those in specific locations in the uterus can have major effects on women’s health. Although the usual leiomyoma does not present a diagnostic problem, its morphologic variants must be clearly identified so as not to misinterpret them as leiomyosarcoma. New treatment protocols have been recently introduced, all of which have had dramatic morphologic effects on the leiomyoma. Some complicate the distinction from malignancy. A number of unusual forms, including some that present outside the uterus, have relationships to estrogen and progesterone receptor. Like other forms described below, they are easily misinterpreted histologically with malignancy. The leiomyosarcoma is the most common of the malignant nonepithelial uterine tumors. This article discusses the diagnostic features of smooth-muscle tumors, with an emphasis on common, problematic, morphologic variants, reviews treatment changes, and emphasizes the distinction among the various lesions (Table 1).

Leiomyoma

Leiomyoma is a benign smooth-muscle tumor that most commonly affects the body of the uterus but may also be found in the cervix, broad ligament, and, rarely, the ovary. This form of tumor can also occur outside of the Mullerian tract, where pathologic criteria for diagnosis differ significantly.

Frequency. The true prevalence of uterine leiomyomas, or fibroids, as they are colloquially known, is uncertain, even though they are the most frequent tumor found in the female genital tract. There are present in 20–30% of women over 30 years of age (1), rising to more than 40% in those over 40 years old (2). In one study, 69% of 1,245 women who underwent hysterectomy for noncancerous conditions had leiomyomas (3). Many women present because of the symptoms caused by the tumors, but there can be no doubt that a high proportion of women harbor leiomyomas completely without symptoms.

The prevalence of uterine leiomyomas varies among ethnic groups. In one study (3), 89% of black women and 59% of white women had leiomyomas in uteri removed at hysterectomy. The black women were, on average, 4 years younger, tended more towards obesity, and had more leiomyomas than white women. Furthermore, the black women were more likely to be anemic and have more severe pelvic pain. This excess rate of uterine leiomyomas cannot be explained by a higher prevalence of risk factors (4).

Etiology. The precise etiology of leiomyomas is unknown, although it is clear that the effects of hormones are pivotal. Leiomyomas are tumors that occur during the reproductive period, a time when hormonal influences are at their maximum. They first become apparent after the menarche, enlarge during pregnancy, and regress after the menopause. Even so, experimental attempts to induce leiomyoma development by the administration of estrogens in animals have failed to produce more than fibromuscular proliferations in the peritoneum. Recent evidence has strengthened the view that estrogens and estrogen receptors play a major role in the genesis of leiomyomas (5). Studies comparing leiomyomas to normal myometrium have shown that leiomyomas have an abnormal gene expression that maintains a high level of sensitivity to estrogen during the estrogen-dominated proliferative phase of the menstrual cycle (1). In addition, cultured cells from leiomyomas have a significantly higher response to estrogen than do matched cultures of myometrial cells from the same patient, particularly if the tissue is taken for culture in the proliferative phase (6). Semiquantitative immunohistochemical demonstration of estrogen and progesterone receptors correlates with the growth rate of the tumors (7).

Further information on the origin of leiomyomas has come from work on their clonality, originally studied using glucose-6-phosphate dehydrogenase isoforms as a marker for chromosomal inactivation. Recent molecular biology techniques have employed methylation differences between the DNA of active and inactive chromosomes (8) and the differential inactivation of the X-chromosome–linked phosphoglycerokinase gene (9). These methods have confirmed that each leiomyoma is clonal and that in patients with multiple uterine leiomyomas, each tumor is clonally independent.

Gross features. Leiomyomas develop everywhere within the myometrium. They may...
occasionally even be seen in the cervix. The most frequent position is within the myometrial wall where, if numerous or large, these intramural leiomyomas can grossly distort the uterus (Figure 1). Those situated close to the endometrium or the serosa are referred to as submucosal and subserosal, respectively. From each of these positions, the leiomyoma may protrude, either into the uterine cavity or into the peritoneal cavity. Those that are sub’s might lead to atrophy or erosion of the mucosal surface and hence intermenstrual bleeding. As a muscular action of the uterus acts to expel the submucosal mass, the leiomyoma becomes pedunculated, giving rise to a fibroid polyp or a submucosal pedunculated leiomyoma. The former may be subjected to further traction by isthmic contractions and may present at the external cervical os, often with an infarcted tip. These women often report cramps not unlike the Braxton Hicks contractions seen in mid- to late pregnancy.

The cut surface of a leiomyoma characteristically shows a whorled, spiral pattern of fibers to the naked eye. The leiomyoma is firm and rubbery, and its cut surface both pops up (rises above the cut surface in the unfixed state because of decompression) and resists indentation by the examining thumb or finger, in contrast to leiomysarcoma. It is usually more pale than the surrounding myometrium. One of the most striking features is the very sharp line of demarcation between the tumor and the surrounding myometrium (Figure 2). This forms a plane of cleavage that enables the leiomyoma to be shelled out of myometrium. The loss of this plane of cleavage is an important feature that may offer a clue to the pathologist that malignant change has occurred, or that a different diagnosis should be entertained, e.g., adenomyoma.

**Microscopic features.** The sharp demarcation from the surrounding myometrium noted macroscopically is also prominent microscopically. The smooth-muscle cells are marked elongated and have eosinophilic cytoplasm and elongated, cigar-shaped nuclei (Figure 3). In an uncomplicated leiomyoma the nuclei are uniform and mitotic figures absent or sparse. Abundant reticulin is present. The smooth-muscle cells of a leiomyoma are usually more closely packed than those of the surrounding myometrium, so that the tumor appears more cellular, a feature that is often particularly striking in women past the menopause. With estrogen withdrawal and the shrinkage of the uterus that occurs after the menopause, the amount of cytoplasm in the smooth-muscle cells of the normal myometrium and in the leiomyoma diminishes dramatically so that the entire tissue appears richer in nuclei. This change is usually more noticeable in the leiomyoma than in the surrounding muscle.

**Degenerative Changes in Leiomyomas**

A variety of degenerative changes are encountered in leiomyomas. The larger the leiomyoma, the more likely it is that some form of degeneration will be present. The most common form of degeneration is hyaline degeneration. The smooth-muscle cells are replaced by collagen with a uniform, pale, eosinophilic, ground-glass appearance. The blood vessels within an area of hyaline necrosis undergo the same change and can be seen as pale outlines, a point of distinction from the coagulative tumor cell necrosis that is seen in leiomysarcoma, where the vessels are often preserved (10). The terms mucoid and myxoid degeneration, with or without cystic change, describe changes that are often associated with hyaline change, and have little further practical importance. Red degeneration (necrobiosis), on the other hand, is a form of degeneration that occurs commonly in pregnancy, and the process is often the cause of pain and fever. The cut surface takes on a more homogeneous look, with loss of the whorled appearance. The color becomes a deeper pink or red and the consistency softer (Figure 4). The color change is due to staining by fresh blood pigment. Unlike hyaline change, the microscopic appearance in red degeneration shows the ghosts of the muscle cells and their nuclei. Later, the periphery of a leiomyoma that has undergone red degeneration may become white and calcified. Calcific degeneration, on the whole, is seen more often in women after the menopause.

**Treatment with Gonadotropin-Releasing Hormone Analogs**

In recent years, gonadotropin-releasing hormone analogs or agonists (GnRHa) have been used to treat uterine leiomyomas. During treatment both the uterus and the leiomyomas decrease in size, but most of the latter return to their original size once the treatment is stopped or within a year even if treatment is continued.

**Table 1. Classification of smooth-muscle tumors.**

<table>
<thead>
<tr>
<th>Type of Tumor</th>
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<tbody>
<tr>
<td>Leiomyoma</td>
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<tr>
<td>Variants of leiomyoma</td>
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<tr>
<td>Cellular leiomyoma</td>
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<tr>
<td>Epithelioid (pleomorphic, leiomyoblastoma, clear cell)</td>
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<tr>
<td>Hemorrhagic cellular leiomyoma</td>
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<td>Lipoleiomyoma</td>
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<tr>
<td>Symplastic (atypical or bizarre)</td>
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<tr>
<td>Smooth-muscle tumors of uncertain malignant potential (a term to be discouraged)</td>
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<tr>
<td>Leiomyosarcoma</td>
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<tr>
<td>Variants of leiomyosarcoma</td>
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<tr>
<td>Epithelioid</td>
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<tr>
<td>Myxoid</td>
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<tr>
<td>Other smooth-muscle neoplasms</td>
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<tr>
<td>Benign metastasizing leiomyoma</td>
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<tr>
<td>Diffuse leiomyomatosis</td>
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<td>Disseminated peritoneal leiomyomatosis</td>
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<td>Intravenous leiomyomatosis</td>
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**Figure 1.** Multiple leiomyomas. On cut section, the tumors are well circumscribed, bulging above the cut surface. These leiomyomas are intramural and one is submucosal. A prolapsed, submucosal leiomyoma protrudes into the endocervical canal. Reprinted from Robboy and Ellington (55) with permission of Gyn-Path Associates.

**Figure 2.** Submucosal leiomyoma. The sharp line of demarcation between the leiomyoma and the surrounding myometrium is clearly shown. In this submucosal position, the overlying endometrium is compressed and atrophic, which often leads to a complaint of bleeding. Reprinted from Robboy and Ellington (55) with permission of Gyn-Path Associates.

**Figure 3.** Leiomyoma, microscopic appearance. Reprinted from Robboy and Ellington (55) with permission of Gyn-Path Associates.
Treated leiomyomas have a significant increase in estrogen receptor content. The GnRH analogues are used mostly as an adjunct to surgery, reducing the need for transfusion, and perhaps permitting vaginal hysterectomy to be performed because of the shrinkage of the leiomyomas (11). The treatment may also be used in perimenopausal women as a temporary measure to reduce menorrhagia prior to the onset of the menopause.

After GnRHα treatment, the entire tumor may become necrotic, in which case the leiomyoma is soft and exhibits a dusky or red color. The appearance seen more commonly is of partial necrosis, with well-delineated red zones within the leiomyoma.

The most striking microscopic feature after GnRHα treatment is coagulative necrosis (12). This may affect a small group of cells or extensive areas within the leiomyoma and be surrounded by a rim of inflammatory cells. Apoptosis may be prominent (13). Changes in cellularity are not significant; both decreased (14) and increased cellularity (12) have been reported. A massive lymphocytic infiltration (15,16) and thickening of blood vessel walls with narrowing of the lumen may also be seen (14). There is no correlation among size of leiomyoma, type of surgery, or length of time between stopping treatment and surgery. A study of cell proliferation indices (Ki67 and proliferating cell nuclear antigen) suggests that the reduction in size of leiomyomas treated by GnRH agonists is due to a reduction in the number of cycling cells, secondary to reduced levels of estrogen and progesterone receptor (17).

Treatment by Arterial Embolization

A further conservative method of treating uterine leiomyomas is by selective arterial embolization (18–21). The procedure is performed under local anesthesia and involves femoral artery puncture with catheterization of the hypogastric then uterine arteries. Polyvinylformaldehyde particles, 150–600 µm in diameter, are introduced until complete devascularization of the leiomyomas is achieved. The pelvic pain that follows lasts 12–18 hr. The leiomyomas undergo coagulative necrosis and eventually hyalinize. About 80% of women who undergo embolization have sufficient improvement in symptoms to avoid subsequent surgical treatment (18).

Variant Forms of Leiomyoma

Cellular Leiomyoma

The cellular leiomyoma is a benign smooth-muscle tumor that has an increased number of cells per unit area when compared with the surrounding myometrium. The gross and microscopic features are often similar to the usual leiomyoma. The most striking difference between a cellular leiomyoma and the usual leiomyoma is that the former is characteristically soft, a feature that this tumor has in common with some leiomyosarcomas. Soft fibroids must always be sampled extensively and, as with all smooth-muscle tumors, preferentially from the perimeter.

The cells comprising this variant are similar to those seen in an ordinary leiomyoma and range from spindle-shaped to round, depending on the angle at which they are sectioned. They have scanty cytoplasm and are very closely packed, so the section is dark blue. A fascicular pattern is present in some areas. The blood vessels are typically large with thick muscular walls, and cleftlike spaces are often seen, possibly representing compressed vessels or edema (22). Unlike the usual type of leiomyoma, cellular leiomyomas often show focal extensions into and appear to merge with the adjacent myometrium. The mitotic count is variable but usually low.

The cellular leiomyoma must be distinguished from leiomyosarcoma and endometrial stromal tumors. The cellular leiomyoma lacks the coagulative tumor cell necrosis, nuclear atypia, and mitotic activity characteristic of a leiomyosarcoma.

Hemorrhagic Cellular Leiomyoma

This variant, also referred to as apoplectic leiomyoma, occurs in pregnancy and during oral contraceptive treatment and is characterized by hemorrhage and cystic change (23,24). There is some overlap with the changes of GnRHα therapy. Grossly, one or more leiomyomas show areas of hemorrhage with cystic change. Microscopically, the smooth muscle is densely cellular, surrounding irregular to round zones of hemorrhage or cystic change. Mitotic activity may be increased [up to as many as 8 mitotic figures per 10 high-power fields (hpf)], but there is no atypia. Vascular changes may also be prominent. Because of the combination of coagulative necrosis with elevated mitotic rates, this variant can be easily mistaken for leiomyosarcoma.

Symplastic Leiomyoma

This smooth-muscle tumor is defined by the presence of variable numbers of smooth-muscle cells with multiple, gigantic nuclei with abundant nuclear chromatin in an otherwise typical leiomyoma.

Grossly, nothing typically distinguishes a symplastic leiomyoma from the usual type of leiomyoma. Microscopically, there are foci of bizarre and pleomorphic tumor cells with atypical nuclei (Figure 5). Most of the bizarre cells are multinucleated or have multilobed nuclei, but greatly enlarged mononuclear cells are also seen. Most of the nuclear features appear to be degenerative, with smudged chromatin, vacuolization, and pyknosis. Most tumors also contain some cells with nuclear features that are more disquieting, where the chromatin is coarsely clumped or granular, with areas of clearing and enlarged nucleoli (25). The multinucleated cells may be found focally, multifocally, or diffusely throughout the neoplasm, and occupy more than 25% of the tumor in most cases. These tumors often show degeneration, edema, and hyaline change, but no coagulative tumor cell necrosis (25,26), with the symplastic cells predominantly at the edge of the degenerating areas. Mitotic figures are often lacking, but up to 7 per 10 hpf have been reported (25,27). They are, however, never atypical. All are benign. The recognition of this leiomyoma variant is critical, as the marked nuclear atypia can lead to an incorrect diagnosis of leiomyosarcoma.

Diffuse Leiomyomatosis of the Uterus

Diffuse leiomyomatosis is a rare condition in which hundreds of small ill-defined leiomyomatous nodules diffusely enlarge the uterus (28–31).

The uterus is symmetrically enlarged and may reach considerable dimensions up to as much as 1 kg (29). The serosal surface is bosselated (31). The nodules, which range from microscopic to 2–3 cm in diameter, are paler than the surrounding myometrium and often present a whorled or trabeculated appearance that may resemble adenomyosis (31).

The nodules are composed of uniform, benign, cellular smooth-muscle bundles that...
are less well defined than usual uterine leiomyomas. They merge with each other and with the surrounding less-cellular myometrium. Mitotic figures are rare and atypia is lacking. Leiomyomas of the usual type may be present in the same uterus.

**Unusual Growth Patterns of Leiomyomas**

Leiomyomas may have a number of special and unusual growth patterns. These are intravascular leiomyomatosis, benign metastasizing leiomyoma, disseminated peritoneal leiomyomatosis, and diffuse leiomyomatosis. They are all rare phenomena.

**Intravascular Leiomyomatosis**

This term describes morphologically benign smooth muscle present within the lumens of veins. Intravenous leiomyomatosis commonly involves extension of the intravascular element beyond the confines of the leiomyoma, 80% spreading outside the uterus into the pelvic veins and, occasionally, along the inferior vena cava and even into the chambers of the heart (32,33).

Intravascular leiomyomatosis is usually apparent on gross examination. The uterus is enlarged and when cut across the intravenous elements may pop up as wormlike coils of firm, rubbery tissue.

Intravenous leiomyomatosis is distinguished from leiomyosarcoma by its lack of mitotic activity, atypia, and coagulative necrosis, and from endometrial stromal sarcoma by the demonstration that it is composed of smooth muscle.

The patients present with the same symptoms as women with ordinary leiomyomas. The condition is seen most frequently in women over 50 years of age. Treatment is by total hysterectomy and bilateral salpingo-oophorectomy, along with removal of as much of the extrauterine elements may pop up as wormlike coils of firm, rubbery tissue.

Intravenous leiomyomatosis is generally harmless condition; the only deaths reported have been associated with intracardiac involvement.

**Benign Metastasizing Leiomyoma**

This is a very rare phenomenon in which histologically benign smooth-muscle tumors are present at distant sites, particularly the lungs, in women who have histologically benign leiomyomas of the uterus (35–38). A high proportion of women with benign metastasizing leiomyomas had a prior dilatation and curettage, myomectomy, or hysterectomy, raising the possibility that surgery had predisposed to the subsequent spread.

Further evidence supporting benign metastasizing leiomyoma as a genuine phenomenon is that primary smooth muscle tumors of the lung are exceedingly rare and that estrogen receptors and a response to hormone treatment have been demonstrated in the pulmonary component. Treatment is by the removal of as much of the metastatic tumor as is feasible, but hormonal treatment using progestins (39) or luteinizing hormone-releasing hormone analogs (40) has also been tried. Progression is very slow. The nomenclature is extremely confusing. A metastasizing smooth-muscle tumor is, of course, biologically malignant regardless of its benign histologic appearance. The existence of this entity simply indicates that our criteria for predicting the behavior of uterine smooth-muscle tumors is imperfect.

**Disseminated Peritoneal Leiomyomatosis**

In this rare entity, multiple small, nodular deposits of histologically benign smooth muscle are found in the superficial subperitoneal tissues, including the serosa of the uterus, tubes, and ovaries (41–43). The condition affects women of reproductive age and there is a strong association with hormonal stimulation. Seventy percent of the patients are pregnant or puerperal at the time of diagnosis or are taking oral contraceptives. Similar appearances have been produced experimentally in animals by administration of estrogen alone or in combination with progestins. The distribution of the lesions seems to be more compatible with a multicentric origin in situ than with metastasis by lymphatic or vascular pathways. Ultrastructural studies indicate that the condition probably involves metaplasia of subperitoneal mesenchymal stem cells to smooth muscle, fibroblasts, myofibroblasts, and decidual cells. As disseminated peritoneal leiomyomatosis generally follows pregnancy, the condition may represent fibrosis and smooth-muscle metaplasia of nodules of decidua. However, a study analyzing clonality by X chromosome inactivation using polymerase chain reaction has shown that, in each of the four patients studied, the same parental X chromosome was nonrandomly inactivated in all the peritoneal tumors, indicating all of the tumors were clonally related (44). This finding would not be expected if the condition were metaplastic, but it is consistent with either a metastatic origin from a single primary tumor or selection for an X-linked allele in clonal multicentric lesions.

The condition is an incidental finding, and nearly all reported cases have run a benign course, undergoing spontaneous regression confirmed by second-look procedures. Nevertheless, six cases of malignancy have developed in diffuse peritoneal leiomyomatosis (45–49). One of the patients developed bony metastases and died within 2 years (45).

**Leiomyosarcoma**

The leiomyosarcoma, a malignant tumor composed entirely of smooth muscle, is the malignant counterpart of the leiomyoma and is the most common pure sarcoma of the uterus.

The incidence is 0.67/100,000 women years. The relative frequency of leiomyosarcoma to leiomyomas is estimated to be as low as 0.13%, which is probably close to being realistic. Upper limits have been given of 6%, a 50-fold variation that probably reflects both differing diagnostic criteria and biases based on referral centers. The age of women with leiomyosarcoma is about 10 years older than those with leiomyoma, most women being older than 40 years. The tumor is more common in black women than in white women. There also may be some relation to estrogen usage, in particular with tamoxifen therapy for breast cancer (50–52).

The gross appearance of leiomyosarcoma often differs significantly from that of a leiomyoma. Most leiomyosarcomas irregularly invade the adjacent myometrium and have a cut surface that is pale with areas of hemorrhage and necrosis. A valuable feature is the loss of the sharp line of demarcation that separates tumor from the normal myometrium (Figure 6). As malignant tumors do not show the decompressive force of the benign tumors, they do not bulge above the cut sur-
face. Consistency is also a useful indicator of malignant change. Unlike leiomyomas, which are firm and rubbery, leiomyosarcomas are softer and less resilient, permitting the examining thumb to push into them.

Compared with leiomyomas, leiomyosarcomas microscopically are generally more densely cellular (Figure 7). The degree of smooth-muscle differentiation is variable. Well-differentiated leiomyosarcomas are composed of elongated smooth-muscle cells with regular nuclei little different from those of leiomyoma. At the other end of the spectrum, a poorly differentiated leiomyosarcoma is composed of rounded and pleomorphic cells with virtually no resemblance to normal smooth-muscle cells. Nuclear as well as cellular pleomorphism, nuclear hyperchromasia, and giant cells also exemplify increasing anaplasia of the tumor. Areas of coagulative necrosis and hemorrhage, sometimes obvious to the naked eye, are also seen microscopically. Mitotic activity is also required for the diagnosis (see below).

**Histological diagnosis of leiomyosarcoma.** Much has been written about the histological criteria for the diagnosis of leiomyosarcoma and its distinction from leiomyoma. Features that play a part in this differential diagnosis include mitotic activity, nuclear atypia, coagulative necrosis, degree of cellularity, degree of differentiation, the presence of tumor giant cells, vascular invasion, and invasion of the surrounding myometrium.

Studies during recent years have shown that additional criteria beyond mitotic rate improve the distinction from leiomyoma. Earlier works emphasized the value of the mitotic count and set 10 mitotic figures per 10 hpf as the threshold for the diagnosis of sarcoma. Since then, many accounts have been published in which the diagnosis has been made almost exclusively by mitotic count, some authors maintaining that any smooth-muscle tumor having 10 or more mitotic figures per 10 hpf is a leiomyosarcoma, regardless of the degree of atypia.

The two extremes are easy to diagnose. If a smooth-muscle tumor is well circumscribed, it is composed of cells that are uniform in size and shape, has no intravascular component, lacks cytological atypia and necrosis, and the mitotic index is less than 5 mitotic figures per 10 hpf, then the tumor is a leiomyoma. On the other hand, if the tumor has infiltrative margins and marked cytological atypia and coagulative tumor cell necrosis, the mitotic index is greater than 10 mitotic figures per 10 hpf, and there are abnormal mitotic figures, then the tumor is a overt leiomyosarcoma. The problems arise when intermediate combinations of these criteria are encountered. A tumor may have substantial cytological atypia but a mitotic index between 5 and 10 mitotic figures per 10 hpf. Alternatively, the mitotic index may be about 10 mitotic figures per 10 hpf, but there may be minimal cytologic atypia. It is now recognized that of the many histological features that can be assessed, mitotic index, the degree of cytological atypia, and the presence or absence of coagulative tumor cell necrosis are the most important predictors of behavior (10).

The employment of three variables in the assessment of smooth-muscle tumors eliminates complete dependence on mitotic count. Smooth-muscle tumors that show no or mild atypia and no coagulative tumor cell necrosis are leiomyomas, irrespective of mitotic count. On the other hand, tumors that show diffuse moderate or severe atypia and have coagulative tumor cell necrosis are leiomyosarcomas. Only intermediate tumors need a mitotic count. This approach allows classification of most tumors that have been previously referred to as smooth-muscle tumors of uncertain malignant potential.

A slightly different approach to assessing the factors that relate to malignancy in smooth-muscle tumors of the uterus was taken in a study analyzing metastatic leiomyosarcomas (53). This study showed that, in addition to mitotic activity greater than 5 per 10 hpf, significant atypia, and coagulative tumor cell necrosis, the finding of a tumor larger than 3 cm in diameter and, to a lesser extent, patients over 50 years of age were factors associated with metastasis and mortality.

Image 48x518 to 213x726

In devising a diagnostic strategy for assessing smooth-muscle tumors, a broad view is important that takes into account all relevant histological features. The age of the patient, the size of the tumor and its gross appearance, as well as the pattern of the tumor margin and vascular invasion assessed microscopically must be considered. Table 2 uses all these features in a strategy that separates the clearly benign from the clearly malignant tumors and gives guidance for the intermediate groups (54).

**Molecular biology of leiomyosarcoma.** Clearly, predicting the behavior of uterine smooth-muscle tumors may be difficult when using conventional histopathological techniques. There is hope that the rapidly developing field of molecular biology may provide additional and perhaps more reliable criteria to help in the management of women with these enigmatic tumors. The area of molecular alterations in the development of smooth-muscle tumors is the theme of other sessions of this symposium, and therefore are addressed elsewhere.

**REFERENCES AND NOTES**


