SMOOTH MUSCLE TUMORS OF THE FEMALE GENITAL TRACT

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KEYWORDS

• Leiomyoma • Atypical leiomyoma • STUMP • Leiomyosarcoma
• Disseminated peritoneal leiomyomatosis • Benign metastasizing leiomyoma
• Intravenous leiomyomatosis • Lymphangioleiomyomatosis • PEComa • Vulva
• Vagina • Uterus • Ovary • Female genital tract

ABSTRACT

Smooth muscle tumors are the most common among mesenchymal tumors in the female genital tract. The vast majority of these neoplasms are clinically benign and easy to diagnose. In contrast, leiomyosarcomas are highly aggressive tumors that may pose considerable diagnostic problems when they display unusual (myxoid or epithelioid) morphology, ambiguous histologic features for malignancy, or an unusual anatomic distribution. Diagnostic criteria for these problematic tumors vary depending on the site and type of histologic differentiation, and are based on a combination of 3 major criteria: (1) moderate to severe cytologic atypia; (2) increased mitotic index; and (3) tumor cell necrosis. Certain benign smooth muscle proliferations may show worrisome histologic features or unusual growth patterns, causing concern for leiomyosarcoma. Furthermore, other tumors, including perivascular epithelioid tumors, may mimic leiomyosarcoma. Careful attention to the clinical and anatomic setting, cytologic and architectural features, and immunohistochemical characteristics are helpful in distinguishing these entities. This article discusses conventional smooth muscle tumors as well as unusual subtypes, with emphasis on the diagnostic criteria and problems in differential diagnosis that arise at each site within the female genital tract.

OVERVIEW

Most smooth muscle tumors in the female genital tract are easily recognized and are benign (leiomyoma).[†] Malignant smooth muscle tumors (leiomyosarcoma) are much less common, but when they occur, most are large, fleshy tumors with variable areas of necrosis and hemorrhage, and they have obvious histologic features of malignancy. Diagnostic problems arise when these tumors exhibit ambiguous histologic features of leiomyosarcoma or unusual anatomic distribution or when conventional (spindled) differentiation is absent.[1] Efforts to correctly diagnose and classify neoplasms exhibiting smooth muscle differentiation anywhere in the female genital tract are directed toward 3 goals:

1. Distinguishing clinically malignant (leiomyosarcomas) from benign neoplasms (leiomyomas)

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[†] Leiomyosarcoma represents about 1% to 2% of uterine malignancies and about one-third of uterine sarcomas. Approximately 1 of every 800 smooth muscle tumors of the uterus is a leiomyosarcoma, but fewer than 1% of women thought clinically to have leiomyoma prove to have leiomyosarcoma.

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that may feature one or more of the following: alternative morphologic differentiation (myxoid or epithelioid), increased cellularity, marked cytologic atypia, and necrosis (infarction or hyaline necrosis versus coagulative tumor cell necrosis). Specific criteria for malignancy differ depending on site of origin (eg, uterus, vulva, and ovary).
2. Distinguishing benign or, at most, clinically indolent genital tract smooth muscle proliferations that primarily involve extragenital sites and may be associated with morbidity, but only rarely lead to patient death. These proliferations, which are often incidental findings, can present at high stage or recur after initial presentation at low stage; they include disseminated peritoneal leiomyomatosis, intravenous leiomyomatosis, benign metastasizing leiomyoma, and lymphangioleiomyomatosis.
3. Excluding metastases from other primary sites and histologic mimics; this is a particularly common problem in the evaluation of uterine samplings, myomectomy specimens, and small biopsies from other sites in the genital tract.

The degree of certainty associated with the classification of any smooth muscle tumor in the female genital tract depends on the degree of experience with that entity (ie, uterine leiomyomas are very common and therefore, histologic criteria are well defined and well recognized for most of them, whereas ovarian leiomyomas are relatively rare and experience with these tumors is limited, especially if they exhibit any morphologic deviation from the usual uterine counterpart); the extent to which the specimen under evaluation is representative of the entire tumor (a particular issue with uterine samplings and myomectomy specimens); and the extent to which the tumor exhibits nonambiguous morphologic features or unusual anatomic distribution. Uncommon smooth muscle tumors with scant available follow-up data should be referred to as "with limited experience," whereas those that defy classification using standard criteria are more appropriately labeled as "uncertain malignant potential." Uterine tumors of "uncertain malignant potential" may prove, over time and accumulated experience, to have recurrent (pelvic or intra-abdominal sites) or metastatic (lung, bone, and so forth) potential.

This review discusses the broad categories of smooth muscle tumors that occur in the female genital tract by site as well as by morphologic subtype. Specific diagnostic criteria and key differential diagnoses for each category of smooth muscle tumor are presented, and strategies to resolve diagnostic problems using immunohistochemistry and other ancillary findings are emphasized. In addition, the groups of smooth muscle tumors that are rarely encountered and currently considered to have insufficient outcome data to be diagnosed with any degree of certainty are highlighted.

UTERINE CORPUS

SPINDLED SMOOTH MUSCLE TUMORS

Conventional (spindled) smooth muscle differentiation is recognized by fascicles of elongated, spindled cells with ovoid, blunt-ended (so-called "cigar-shaped") nuclei and eosinophilic cytoplasm that can be highlighted on trichrome stain. The cells express desmin, h-caldesmon, HDAC8, smooth muscle actin, and occasionally, CD10. When CD10 expression is present in a uterine smooth muscle tumor exhibiting usual morphology, it is usually weaker and less extensive than staining for smooth muscle markers, but on occasion the CD10 expression may be as strong and diffuse as desmin expression; in these cases, the classification of the smooth muscle tumor should not be altered unless the tumor exhibits an unusual pattern of differentiation (increased cellularity and so forth). Cytokeratin and epithelial membrane antigen (EMA) expression is often seen in uterine smooth muscle tumors. Almost all benign and low-grade smooth muscle neoplasms in the uterine corpus and elsewhere in the female genital tract express hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]). Uterine smooth muscle tumors with usual and epithelioid morphology may also express HMB-45; a subset of these latter tumors has been classified as uterine perivascular epithelioid tumors (PEComa), although this is a subject of ongoing controversy (see section on PEComa).

CONVENTIONAL (SPINDLED) LEIOMYOMA

This leiomyoma subtype is the most common tumor to occur in the uterus. The lesions are often multiple, and commonly occur in the fourth and fifth decades. An increased incidence is observed in African American women. Up to 75% of hysterectomy specimens contain one or more leiomyomas. Most patients are asymptomatic. Clinical manifestations depend on size, secondary changes, and location, and include pain, abnormal vaginal bleeding, and an abdominal or pelvic mass. Patients rarely present with erythrocytosis or clinical features similar to Meigs syndrome.[2]