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Clinical update of smooth muscle tumors of the uterus

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Abstract. Smooth muscle tumors of the uterus represent a spectrum of diseases that range from benign leiomyoma to malignant leiomyosarcoma. The leiomyoma is the most common of these neoplasms. Clinically, it is important to fully understand the differences in clinical presentation, biologic behavior, and management for patients with benign leiomyoma, smooth muscle tumors of uncertain malignant potential, and leiomyosarcoma. The goal of this review is to present the most recent information about common smooth muscle tumors of the uterus including their etiology, histopathology, radiographic and clinical presentations, and available treatment options.

Smooth muscle tumors of the uterus encompass a variety of neoplasms, benign and malignant. These include leiomyomas and their subtypes, which include smooth muscle tumors of uncertain malignant potential (STUMP) and leiomyosarcomas (Table 1). Uterine leiomyomas are the most common gynecologic neoplasm in women of reproductive age.[1] Diagnosis often is made by appearance on ultrasound and confirmed by histology. It is important to distinguish benign from malignant tumor growth for appropriate treatment. Even though these tumors commonly cause abnormal uterine bleeding, routine endometrial sampling rarely aids in diagnosis for smooth muscle tumors. For patients interested in uterine conservation, advances in minimally invasive therapies have provided alternatives to hysterectomy but often do not provide tissue for definitive diagnosis. Magnetic resonance (MR) imaging may be helpful in triaging patients to appropriate therapy.[2] A study found that signal voids and evidence of prominent vessels on MR imaging are characteristic of vascular lesions. Clear guidelines have yet to be established when using MR imaging to differentiate between leiomyomas and leiomyosarcomas; however, the appearance of invasion, growth, and hemorrhagic necrosis is suggestive of malignancy.[3] Smooth muscle tumors are categorized by the combination of a number of characteristics. We will discuss the important differences in the most common smooth muscle tumors of the uterus and current available therapies.

Clinical and histologic characteristics of smooth muscle tumors

Leiomyoma

Uterine leiomyomas represent a major public health concern secondary to the symptoms produced, such as menorrhagia, infertility, pregnancy loss, and pelvic pain. Approximately one-third of hysterectomies in the United States are

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Table 1 Classification of smooth-muscle tumors

Leiomyoma
Leiomyoma variants
Cellular leiomyoma
Bizarre leiomyoma ("symplastic" "atypical" or "leiomyoma with bizarre nuclei")
Mitotically active leiomyoma
Leiomyoma with hormone-related changes
Myxoid leiomyoma
Smooth muscle tumors of low or uncertain malignant potential
Epithelioid smooth muscle tumors
Smooth muscle tumors with unusual growth patterns
Diffuse peritoneal leiomyomatosis
Intravenous leiomyomatosis
Metastasizing leiomyomas
Leiomyosarcoma
Epithelioid leiomyosarcoma
Myxoid leiomyosarcoma

attributed to leiomyomas. It has been estimated that the incidence of symptomatic tumors in American women over the age of 30 years is approximately 25%. This rises to more than 40% in women over 40 years of age.[1] In fact, an incidence of leiomyomas of 77% was reported in a study that described thorough evaluation of all hysterectomy specimens, regardless of the clinical reasons for performing the hysterectomy. The conclusion was that one cannot rely on the routine pathology report and clinical diagnosis to determine the epidemiology of uterine leiomyomas.[4]

The prevalence of uterine leiomyomas appears to vary among ethnic groups. Uterine myomas were found in 89% of black women and 59% of white women after review of 1245 hysterectomy specimens.[5] In that study, black women were on average 4 years younger at the time of diagnosis, had more leiomyomas than the white women, and tended to have more obesity. Black women also tended to have more pelvic pain and anemia when compared with white women.[5] The evaluation of myomas in other racial groups is understudied.

Etiology

Little is known of the etiology of uterine leiomyomas. Methylation studies have determined that leiomyomas are clonal and that in patients with multiple leiomyomas, the tumors are clonally independent. Leiomyomas often exhibit cytogenetic abnormalities, most commonly involving translocations between chromosomes 12 and 14.[6]

Leiomyomas usually first become apparent after menarche, may enlarge during pregnancy, and regress after menopause. Many studies have demonstrated the presence of steroid hormone receptors and steroid dependence of these tumors. Some theories relate to estrogen and/or progesterone effects, duration of exposure, and tissue sensitivity in the initiation of tumor formation.[6,7] Another interesting theory is that leiomyomas are the product of an altered response to tissue damage or ischemia that may occur with menses and uterine contraction, similar to keloid formation in skin repair.[6] Growth factors, such as insulin-like growth factor-1, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β , have also been implicated in the pathogenesis of leiomyomas.[6] Researchers studied the immunohistochemical parameters basic fibroblast growth factor (bFGF), PDGF, and VEGF in a group of 31 patients treated with gonadotropin-releasing hormone (GnRH) analog therapy and compared them with 55 untreated controls.[8] They found decreased immunoexpression of all three growth factors in treated patients.[8] Microvessel density was analyzed in this study with CD34 and CD105 expression. Treated patients had a statistically significant decrease in both of these parameters.[8] These finding suggest bFGF, PDGF, and VEGF may have a role in the pathogenesis of uterine leiomyomas.

Gross features and clinical presentation

Leiomyomas may develop anywhere in the myometrium and occasionally in the cervix, broad ligament, and ovaries. Most frequently, they develop in the myometrial wall and can lead to uterine distortion (of both the cavity and the overall contour of the uterus) if large and multiple. Those originating close to the endometrium may lead to atrophy or erosion of the mucosal surface, and the patient may develop intermenstrual bleeding and have difficulty achieving pregnancy implantation, leading to miscarriage. The muscular action of the myometrium can act to expel the myoma. The leiomyoma may be pedunculated, giving rise to a myoma polyp or a submucosal mass, presenting as a prolapsed myoma with an eroded tip. These women often report significant uterine cramping and irregular bleeding. Subserosal leiomyomas can become pedunculated, and if they undergo torsion of the pedicle, can become separated from the uterus. Infrequently, some may attach to another pelvic structure (parasitic leiomyoma).[9]

The leiomyoma is firm, rubbery, and glistening. Its cut surface bulges and resists indentation, in contrast to the softer consistency of the leiomyosarcoma. Often, there is a very sharp line of demarcation between the leiomyoma and the surrounding myometrium recognized as a pseudocapsule.[9] During myomectomy, this cleavage plane allows easy dissection of the myoma. The loss of this cleavage plane is an important feature that may offer a clue that the tumor may be malignant. Another suspicious finding for malignancy is that of a single large myoma or a rapidly enlarging myoma. One study evaluated 21 patients with uterine leiomyosarcomas over a 10-year period and found that in 95% of the specimens, the leiomyosarcoma was either the largest or the only mass. The authors recommended monitoring of the largest myoma during conservative therapy.[10]