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Review Article

Uterine Smooth Muscle Tumors: A Review

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Abstract

Uterine smooth muscle tumors heterogeneous tumors include at least six histologically defined tumor types. Smooth muscle tumors are divided into two categories: benign leiomyomas and malignant leiomyosarcomas. Uterine smooth muscle tumors have also morphological variants that are difficult to interpret and identify as benign or malignant called "smooth muscle tumors of uncertain malignant potential". Immunohistochemistry for progesterone receptor and p53 is useful as a supplement to morphological evaluation of uterine smooth muscle tumors that are causing problems. It might be hard to differentiate between endometrial stromal sarcomas and uterine smooth muscle tumors.

Keywords: Uterine smooth muscle tumors, diagnosis, therapy

INTRODUCTION

The most prevalent neoplasm in the female reproductive tract is uterine smooth muscle tumors. These tumors are a group of histologically, genetically, and clinically heterogeneous tumors that include at least six histologically defined tumor types: leiomyoma, mitotically active leiomyoma, cellular leiomyoma, atypical leiomyoma, uncertain malignant potential, and leiomyosarcoma. The nature of these varieties, aside from leiomyoma and leiomyosarcoma, is not fully characterized. There are six primary forms of uterine smooth muscle tumors, each with its own set of gene mutation signatures. Leiomyosarcoma and atypical leiomyoma have a lot of the same chemical changes. The findings show that atypical leiomyoma could be a precursor lesion to leiomyosarcoma or have genetic changes that are similar throughout the early stages of the disease (Zhang et al., 2014). Uterine smooth muscle tumors have morphological variants that are difficult to interpret and identify as benign or malignant. Because of their unpredictable activity and clinical prognosis, these tumors have been called "smooth muscle tumors of uncertain malignant potential" (STUMP) by the World Health Organization (Vilos et al., 2012). The term "smooth uterine muscle of unclear malignant potential" (STUMP) refers to a group of uterine smooth muscle tumors that can't be classified as benign or malignant with certainty. Due to its non-aggressive behavior and longer survival rate than leiomyosarcomas, the diagnosis, surgical care, and follow-up of this tumor remain controversial, especially in pre-menopausal women with fertility desires. Recurrence, on the other hand, is predicted to occur between 8.7% to 11%, and may include delayed recurrences (Dall'Asta et al., 2014). STUMPs are uterine smooth muscle tumors with unclear malignant potential that exhibit pathological traits that prevent an equivocal diagnosis of leiomyosarcoma but do not meet the criteria for leiomyoma or its variations, raising worries that the tumors may behave malignantly. If fertility is lost, total hysterectomy with or without bilateral salpingo-oophorectomy is the conventional therapy, however myomectomy alone can be considered in young individuals who want to save their reproductive potential. A diligent surveillance every six months for the first five years and afterwards once a year is strongly recommended. STUMP patients might relapse as either STUMP or leiomyosarcoma in 11–13% of instances, and their 5-year overall survival rates range from 92 to 100 percent (Gadducci and Zannoni, 2019). Smooth muscle tumors are divided into two categories: benign leiomyomas and malignant leiomyosarcomas. Leiomyosarcomas are soft tissue smooth muscle tumors that have both atypia and mitotic activity, indicating the possibility of metastasis. However, certain tumors fall into neither of these categories, and in these circumstances, the term "smooth muscle tumor with unclear biologic potential" is suitable. With restricted sampling, such as needle core biopsies, this category is frequently used. Smooth muscle hamartoma and angioleiomyoma are benign smooth muscle tumors. In women, estrogen-receptor positive leiomyomas are a specific type of leiomyoma. Similar to uterine leiomyomas, these tumors can develop anywhere in the abdomen and abdominal wall. Leiomyosarcomas can develop in any part of the body, however they are more common in the retroperitoneum and the proximal extremities. They have a smooth muscle cell-like appearance, yet they can undergo pleomorphic evolution ('dedifferentiation'). Smooth

muscle actin is essentially uniformly present, and desmin positive is common. This, together with the lack of KIT expression, distinguishes leiomyosarcoma from gastrointestinal smooth muscle tumors, a serious disease in the soft tissues of the abdomen. Epstein-Barr virus-associated smooth muscle tumors are a subtype of AIDS or post-transplant patients' smooth muscle tumors. Although these tumors may have poor smooth muscle development, nuclear Epstein-Barr virüs-RNA can be used to diagnose them. Smooth muscle tumors' genetics are poorly understood, in contrast to many other soft tissue tumors, and diagnostic testing is not yet widely applied in this histogenetic category. Leiomyosarcomas are known to be genetically complicated, with 'chaotic' karyotypes such as aneuploidy or polyploidy common, and no recurrent tumor-specific translocations have been found (Miettinen, 2014). Smooth muscle tumors of undetermined malignant potential and leiomyosarcomas arising from the Muellerian duct are extremely rare when compared to leiomyomas. Their molecular pathophysiology is still a mystery (Holzmann et al., 2015).

DIAGNOSIS

Benign leiomyomas to malignant leiomyosarcomas are all types of uterine smooth muscle tumors. Numerous molecular investigations have found that leiomyomas and leiomyosarcomas share few mutations and that the majority of tumors originate through separate processes. Histopathological leiomyoma subtypes differ not only from normal leiomyomas, but also from one another, based on the molecular back ground. The discovery of leiomyoma driver mutations in approximately one-third of leiomyosarcomas shows that some tumors emerge from a leiomyoma precursor lesion or that these mutations provide a growth advantage to even the most aggressive cancers. Understanding the molecular underpinnings of diverse smooth muscle tumor subtypes is clinically important since it may lead to improved diagnosis and customized treatments in the future (Makinen et al., 2017). Uterine smooth muscle tumors of uncertain malignant potential (STUMPs) have very little information about their clinical behavior and risk factors. The majority of STUMP patients are of reproductive age (Alper et al., 2015). Smooth muscle tumors with unknown malignant potential are an uncommon type of uterine cancer. Due to the scarcity of descriptions in the scientific literature, their identification using imaging is still limited. Between 2014 and 2019, Cotrino et al. (2020) evaluated preoperative sonographic data of patients receiving a histopathological diagnosis of smooth muscle tumors of uncertain malignant potential at the S. Anna Hospital (Turin, Italy), a tertiary gynecological center, at the S. Anna Hospital (Turin, Italy). On the basis of ultrasound pictures, tumors were classified using words and definitions developed by the morphological uterine sonographic assessment group. A total of fourteen patients with suspected malignant smooth muscle tumors (20 lesions, 18 pure and 2 with concomitant leiomyosarcoma) were detected. Nine (64%) of the patients were of reproductive age, with a median age of 47 years (range 28–77). Six patients (43 percent) had no symptoms, two (14 percent) had abdominal pain, two (14 percent) had menorrhagia, and four (29 percent) had both. Local recurrences of uterine smooth muscle tumor of unknown malignant potential and leiomyosarcoma occurred in two (14 percent) of the patients. Nine (69%) smooth muscle tumors with unknown malignant potential were found to be

weakly or moderately vascularized on ultrasound imaging, with nine (82%) showing both circumferential and intra-lesional flows. Only three people (15%) had shadowing. In seventeen cases (85%), the outlines were well-defined, and the majority (90%) had isoechoic or mixed echogenicity, with microcystic anechoic regions in fourteen cases (70%). The researchers determined that the sonographic features of smooth muscle tumors with unknown malignant potential can vary and that there is no pathognomonic description. The presence of single or many lesions with specific ultrasonography findings, on the other hand, should raise the suspicion of tumors with unknown malignant potential. Isoechogenicity or mixed echogenicity, regular boundaries, presence of internal microcystic and anechoic zones, low to high circumferential and intralesional vascularization, and absence of shadowing are some of these characteristics. Suzuki et al. (2018) investigated a new magnetic resonance imaging (MRI) grading system for preoperative classification between benign and variant-type uterine leiomyomas, as well as smooth muscle tumors with unknown malignant potential (STUMPs). Between January 2012 and December 2014, the medical records of 313 patients who were treated for uterine myomas and diagnosed with variant type leiomyomas or STUMPs (n = 27) or benign, typical leiomyomas (n = 286) were reviewed retrospectively. T2-weighted imaging (high or low), diffusion-weighted imaging (high or low), and apparent diffusion coefficient values (high or low; apparent diffusion coefficient 1.5 103 mm^2/sec was considered low) were used to classify uterine myoma MRIs. Grades I to II were classified as benign or typical leiomyomas, grade III as degenerated leiomyomas, and grades IV to V as STUMPs or variant type leiomyomas. For grades I through V lesions, accuracy values were 98.9%, 100%, 94.3 percent, 58.8 percent, and 41.9 percent, respectively. To distinguish between benign leiomyomas and STUMPs, the grades were separated into two groups (grades I–III were regarded negative, whereas grades IV–V were considered positive). Grades IV to V had a sensitivity of 85.2 percent, a specificity of 91.3 percent, a positive predictive value of 47.9%, a negative predictive value of 98.5 percent, a positive likelihood ratio of 9.745 and a negative likelihood ratio of.162. This new MRI grading system for uterine myomas could help distinguish benign leiomyomas from STUMPs or variant type leiomyomas in the future, and it could be a useful presurgical diagnostic tool. Uterine smooth muscle tumors are diagnosed using a combination of microscopic characteristics. However, a tiny percentage of these tumors continue to be difficult to diagnose. Immunohistochemistry for progesterone receptor and p53 is useful as a supplement to morphological evaluation of uterine smooth muscle tumors that are causing problems (Hewedi et al., 2012). In the occurrence of STUMP, attentive multidisciplinary management is required because to the lack of consensus regarding the malignant potential, diagnostic criteria, gold-standard treatment, and follow-up. From the time of diagnosis to the end of follow-up, a gynecologist, a dedicated pathologist (with a high degree of expertise in gynecological pathology), and an oncologist should collaborate in the counseling and management of this neoplasm. Furthermore, immunohistochemistry should be used to look for p16 and p53 overexpression in order to identify a group of patients who

are at a higher risk of recurrence and could benefit from more aggressive surgical-oncological treatments (Dall'Asta et al., 2014). Smooth muscle tumors of the uterus are a difficult group of tumors to diagnose. There are no reliable molecular surrogate markers for discriminating between benign and malignant tumors. As a result, morphologic criteria are used to make the diagnosis. In morphologically problematic types of leiomyomas, leiomyomas with odd nuclei, and leiomyosarcomas, known FH-deletions, a recurring molecular alteration in leiomyomas, occur. Although MED12 mutations are common in leiomyomas, they are uncommon in leiomyosarcomas and leiomyomas with unusual nuclei. The genetic similarities between leiomyomas with bizarre nuclei and leiomyosarcomas raise the intriguing possibility that uterine leiomyomas with bizarre nuclei and leiomyosarcomas are closely related, challenging the conventional view that a leiomyoma with bizarre nuclei is a tumor with only marked 'degenerative' cellular changes. These findings support the idea that uterine smooth muscle tumors can develop (Liegl-Atzwanger et al., 2016). It might be hard to differentiate between endometrial stromal sarcomas and uterine smooth muscle tumors. Transgelin, a 22-kDa actin-binding protein, has recently been identified as a smooth muscle marker. Transgelin appears to be a highly sensitive and specific marker of smooth muscle development in the uterus, and it could be used to distinguish leiomyosarcomas from endometrial stromal sarcomas. It could be employed as a secondary marker for decision-making, particularly in tumors with a shaky histology (Tawfik et al., 2014). The aetiology of endometriosis remains largely unknown (Yilmaz, 2022). In uterine smooth muscle tumors, the oncogenic phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin pathway (PI3K-AKT-mTOR) is known to be activated, and Stathmin 1 (STMN1) expression has been identified as a marker of PI3K-AKT-mTOR pathway activation. STMN1 is a very sensitive marker for leiomyosarcoma, however it lacks diagnostic specificity. The absence of STMN1 antibody in a putative leiomyosarcoma is a strong argument against this diagnostic potential, hence the 100 percent negative predictive value for leiomyosarcoma may give some diagnostic benefit in a small sample (Allen et al., 2015). The Sonic Hedgehog signaling system (SHH) has been shown to have a key role in carcinogenesis and cellular differentiation in several studies. SHH protein expression can be used to assess the propensity for malignancy in uterine smooth muscle tumors. Furthermore, GLI1 and SMO could be used as future therapeutic targets in the treatment of uterine smooth muscle tumors in women (Garcia et al., 2016).

Hereditary Leiomyomatosis And Renal Cell Carcınoma (HLRCC)

HLRCC (hereditary leiomyomatosis and renal cell carcinoma) is an autosomal dominant familial condition caused by a germline mutation in the fumarate hydratase (FH) gene. It is linked to an increased risk of uterine and cutaneous smooth muscle tumors, as well as renal cell carcinoma. HLRCC-associated RCC develops in up to 25% of patients, generally in the fourth decade, and is characterized by high-stage, aggressive malignancies with a poor clinical prognosis. In the second to third decade, most women with HLRCC develop big and bulky uterine smooth muscle tumors (USMT), providing a good chance for early identification of HLCC and timely

adoption of RCC surveillance. However, because HLRCC is uncommon but USMT is frequent, the idea of screening women with USMT for HLRCC is challenging. Furthermore, spontaneous FH gene aberrations unrelated to HLRCC might cause FH deficit in USMT, confounding any prospective screening approach. Recent research suggests that tumor shape can be utilized to detect FH deficit in USMT patients and so refer them to formal genetic counseling. Staghorn-shaped blood vessels and an alveolar pattern on low magnification should provoke a high magnification examination for eosinophilic cytoplasmic inclusions and oval nuclei with conspicuous eosinophilic macronucleoli surrounded by a halo. Schwannoma-like development and a chain-like distribution of tumor cells are also indicators. Although immunostains for FH and 2SC exist, their utility is restricted when FH defective morphology is well-developed. According to some research, the incidence of germline pathogenic mutations in FH among women with USMT and FH deficient morphology is as high as 50%, with somatic FH mutation accounting for the rest. As a result, morphologic evaluation of USMT for FH deficient features can be used as a screening tool for HLRCC syndrome, with individuals being referred to a formal genetic risk assessment (Garg & Rabban, 2021). A strategy for identifying women at elevated risk for hereditary leiomyomatosis renal cell carcinoma (HLRCC) syndrome has been proposed: pathology-based screening of uterine smooth muscle tumors (uSMT) for morphology suggestive of fumarate hydratase deficiency (FH-d morphology). In otherwise unselected women with uSMT, prospective morphology-based screening combined with referral for genetic counseling can lead to the diagnosis of HLRCC syndrome. This method should be used in the pathologic investigation of all uterine smooth muscle tumors on a regular basis (Rabban et al., 2019).

THERAPY

Immunotherapies that target the PD-1/PD-L1 checkpoint axis for the treatment of mesenchymal neoplasms are gaining popularity. However, in uterine smooth muscle tumors, PD-L1 expression and tumor-associated lymphocytes have not been thoroughly examined. Treatment with targeted immunotherapy may be appropriate in a subset of patients with leiomyosarcoma and maybe other malignancies with ALK rearrangements (Shanes et al., 2019). Hypoxia-related angiogenesis mechanisms are crucial for uterine smooth muscle tumors. Vascular endothelial growth factor, hypoxia inducible factor 1, T-cell intracellular antigen1 (TIA1), eukaryotic translation initiation factor 2 (eIF2), and thrombospondin 1 are all associated to angiogenesis during hypoxia (TSP1). eIF2 and TIA1 have been shown to inhibit hypoxia inducible factor 1 protein synthesis. Vascular endothelial growth factor can also be induced by mechanisms other than hypoxia inducible factor 1, such as COX2, Ras, NF-B, or c-myc. Anti-angiogenic therapy could be effective in the treatment of tumors since angiogenesis can induce and accelerate tumor development (Uluer et al., 2015).

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