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Uterine Mesenchymal Tumors from a Gynaecological Point of View: A Mini-Review

Mini Review

Dr. Huseyin Aydogmus, Dr. Servet Gencdal, Dr. Nihan Gencdal and Dr. Serpil Aydogmus*

Department of Obstetrics and Gynecology, Izmir Katip Celebi University, School of Medicine, Turkey

***Corresponding Author:** Dr. Serpil Aydogmus, Department of Obstetrics and Gynecology, Izmir Katip Celebi University, School of Medicine, Turkey.

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Mesenchymal tumors of the uterus comprise a heterogeneous group which may pose occasional diagnostic challenges. Smooth muscle and endometrial stromal tumors constituting the majority of the group usually show homologous mesodermal differentiation, however heterologous elements such as bone, cartilage, or skeletal muscle are not rare. Distinction of these tumors as benign or malignant is vital in determining clinical prognosis. However, despite utilization of various immunohistochemical stains histologic diagnosis might be challenging [1]. This paper aims to review mesenchymal tumors of the uterus from a gynaecological point of view.

Mesenchymal tumors are either benign or malignant and are classified according to the tissue of origin as smooth muscle tumors, endometrial stromal tumors, and subclassified further into their growth pattern variants.

Smooth Muscle Tumors

Leiomyoma, is one the most common visceral tumors of the human body. Clinical presentations vary depending on the location and size. Submucosal leiomyomas tend to present with abnormal uterine bleeding as well as prolapse into the vagina, in which case they should be differentiated from cervical and endometrial polyps, carcinomas, and sarcomatous pathologies. Histologically they are composed of monotonous smooth muscle bundles similar to the surrounding myometrium. These microscopic features may easily be recognised by an experienced gynaecopathologist. Number of mitoses, presence of cellular necrosis and nuclear atypia are distinctive histologic features from leiomyosarcoma [2,3]. While benign variants of leiomyoma occur 1/100, leiomyosarcoma occurs 1/500.

Mitotically active leiomyoma is a small, hypercellular, and almost always benign variant with 5 - 15 mitoses in 10 high power fields (HPFs) but without any atypia or necrosis. The mitotic index is affected by the hormonal state. Higher mitotic activity is reported in myomas excised during the secretory phase, gestation, and exogenous progesterone treatment [4]. Clinical management is same as the standard leiomyoma.

Myxoid leiomyoma contains abundant extracellular stroma. Although no malignant potential has been defined, it is important to be aware of the malignant forms in differential diagnosis.

Epithelioid leiomyoma is exceedingly rare. Neoplasms with perivascular epithelioid cell differentiation (PEComas) should also be considered in the differential diagnosis of epithelioid smooth muscle cell tumors.

Plexiform leiomyoma is composed of interlacing bands and bundles of smooth muscle cells embedded in dense extracellular matrix. It is often associated with intravenous leiomyomatosis and has a semi-malignant behaviour.

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Leiomyoma with heterologous elements (lipoLM) is histologically a combination of smooth muscle and mature adipose tissue in variable proportions. It is mostly asymptomatic and reported in obese, postmenopausal women aged between 50 and 70. Despite its benign behaviour 18.8% of cases are accompanied by concurrent gynaecological malignancies [5].

Cellular (highly) leiomyoma is defined as a tumor of increased cellularity compared to the neighbouring myometrium. Although it is considered benign, aggressive behaviour might be observed in cases with chromosome 1p deletion. Histologically it can be confused with endometrial stromal sarcoma [6]. It has the same clinical approach as the STUMP.

Dissecting leiomyomas are nodular smooth muscle tumorlets surrounded by hydropic matrix that may invade surrounding tissues and even extend beyond the uterus. Clinical approach is similar with classical leiomyoma.

Pleomorphic and symplastic leiomyoma has been renamed as "Leiomyoma with bizarre nuclei" by World Health Organization (WHO) [7,8]. Focal or diffuse atypia might be observed. High cure rates are only observed following surgery. Clinical management is similar with STUMP.

Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP) are rare tumors that share some common histological features with sarcomas but fail to fulfil their diagnostic criteria. Although coagulation necrosis is the most important predictor of malignant behaviour, clinical prognosis is not predictable. Smooth muscle tumors with high mitotic rates (>15 per 10 HPFs) might be classified in this group due to their rarity and unpredictability. Clinical findings are similar to that of myomas and endometrial carcinomas, with a recurrence rate of 17%. Annual follow-up by clinical and imaging methods is recommended in cases diagnosed by hysterectomy [9].

Leiomyosarcoma (LMS) comprises 25% of all uterine mesenchymal tumors and is one of the most common uterine malignancies. Despite the resemblance of clinical findings to leiomyoma, it is more frequent after the 4th decade. It usually presents as an irregular mass greater than 10 cm with hemorrhagic and necrotic areas on cross-section. Histologically it is characterized by an increased mitotic rate (>10 mitoses/10 HPFs), diffuse nuclear atypia and coagulative tumor cell necrosis [10].

Epithelioid LMS is defined as LMS with > 5 mitoses/10 HPFs which is histologically characterized by round-polygonal cells with eosinophilic or clear cytoplasm. The absence of necrosis does not indicate benign behaviour.

Myxoid LMS: Myxoid nature might lead to difficulties in determining the grade of pleomorphism, smooth muscle origin, and true mitotic count. A quite aggressive clinical prognosis is not rare.

LMS with giant cells

Benign Uterine Variants with Extrauterine Disease resemble a leiomyoma with its histologic features despite its semi-malignant character. It is reported during reproductive years and has a good response to anti-estrogen treatment [11].

Intravascular Leiomyomatosis demonstrates histologic features of benign smooth muscle tumors, nonetheless distant metastasis up to the heart via uterine and pelvic veins may be observed. Literature search reveals less than 150 cases. It might rarely be seen in postmenopausal patients. Recurrences, namely pulmonary, have been reported 7 - 14 years after hysterectomy [12,13].

Diffuse Peritoneal Leiomyomatosis is a rare phenomenon characterized by multiple nodules in pelvic and peritoneal surfaces that might be confused with ovarian-peritoneal malignancies. Malignant transformation (< %5) might be observed [14].

Benign Metastasizing Leiomyoma is quite rare, merely 150 cases are found in the literature. It presents as leiomyoma-like solitary nodules in different locations remote from the uterus, lungs being the most frequent. Molecular studies revealed a monoclonal structure not different than classical leiomyomas. Presentation might either be asymptomatic or with respiratory symptoms [15,16].

Endometrial Stromal Tumors

Tumors originating from endometrial stroma are subgrouped as benign endometrial stromal nodule, low grade endometrial stromal

sarcoma and undifferentiated endometrial stromal sarcoma. They are usually seen in postmenopausal women in 4th and 5th decades. Abnormal vaginal bleeding and pain are the most common symptoms [17]. Although clinical presentation is generally is in the form of an abnormal uterine bleeding, endometrial biopsy alone is not enough for diagnosis. If the diagnosis has been made prior to hysterectomy preoperative imaging techniques are recommended to detect metastatic spread. In the absence of extra-abdominal tumor spread cytoreductive surgery leaving as little as possible residual tumor is recommended while in the presence of extra-abdominal tumor medical adjuvant therapy is the first-line of treatment [18]. Utilization of imaging techniques to detect extrauterine metastasis is recommended in cases diagnosed after hysterectomy. Since the advantages of lymphadenectomy in uterine sarcomas are controversial, complementary surgery is generally not recommended [19].

Endometrial Stromal Nodule is the rarest of endometrial stromal neoplasia. Differentiation from sarcomas, other malignant tumors, or leiomyoma via imaging techniques is not possible. Histologic diagnosis might be challenging as well. It is usually characterized by a dense, regular cellular proliferation similar to proliferative endometrial stroma, peri-arteriolar cellular aggregates and low mitotic activity (< 3MF/10 HFP). Foamy histiocytes, lymphocytic infiltrates, and hyalinization are also common. A sharp demarcation from the surrounding myometrium is notable [20,21].

Low Grade Endometrial Stromal Sarcomas are low grade tumors with metastatic potential. Invasive, finger-like projections extending into the myometrium, veins, and lymphatics are characteristic. Histologically it consists of dense, uniform stromal cells which may show minimal cellular pleomorphism, slight nuclear atypia, and seldom mitotic activity. Diverse morphologic presentations such as fibrous, myxoid, glandular or smooth muscle might be challenging for diagnosis [22]. Majority of this group of tumors are hormonally active (ER and PR+). They are immunohistochemically negative for stains CD10, desmin and h-caldesmon. Although specific translocations such as t(7;17), presence of JAZF1 and JJAZ1 gene positivity are helpful differential features in diagnosis, diverse morphologic presentations pose difficulty in diagnosis [23].

Undifferentiated Endometrial Sarcoma is characterized by prominent cytologic atypia, nuclear pleomorphism, and widespread invasion. Normal endometrial tissue properties are absent while hemorrhage and necrosis are frequent. Destructive myometrial invasion is notable [24]. They show strong positivity for proliferation markers such as Ki67, p16 and p53, and moreover express receptor tyrosine kinase CD117 (c-KIT) and human epidermal growth factor receptor 2 (HER2 or ERBB2). Usually there is no immunoreactivity for ER, PR, desmin or smooth muscle actin (SMA) [25].

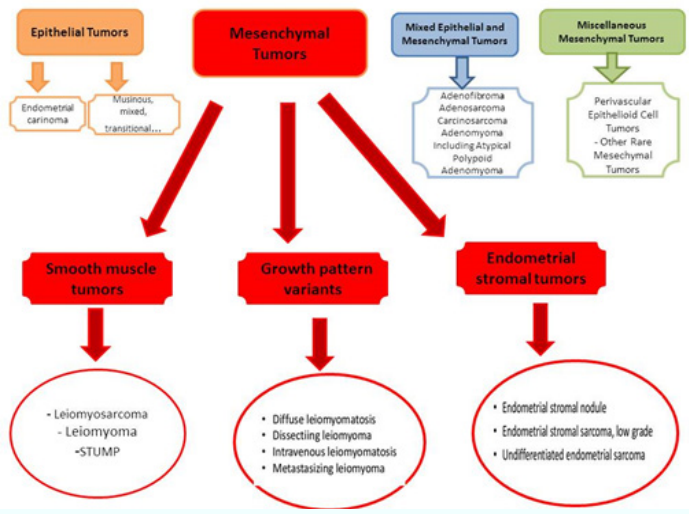

Figure 1: *Mesenchymal tumors of the uterus.*

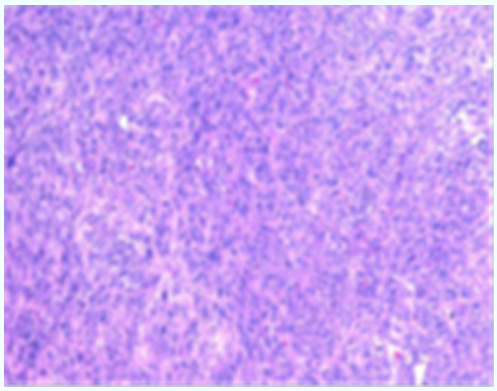

Figure 2: *Hypercellularity.*

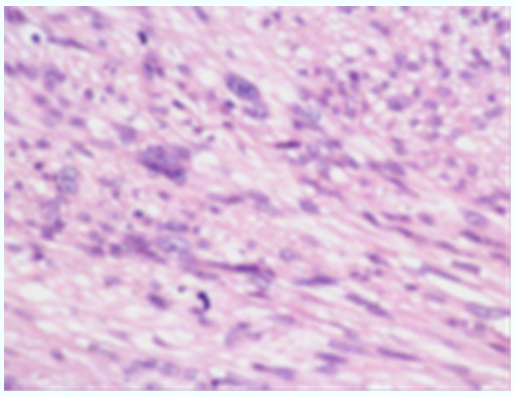

Figure 3: *Focal atypia.*

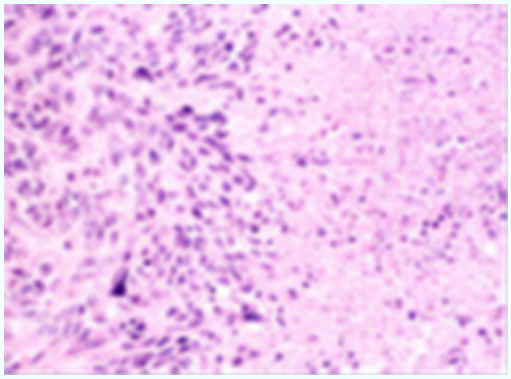

Figure 4: *Tumor cell necrosis.*

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