

Diagnostic and prognostic implications of mast cell microenvironment in smooth muscle tumors of the uterine corpus

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ABSTRACT

Mast cells can be found almost everywhere throughout the human body, even in some benign soft tissue tumors (e.g. neurofibroma) and their presence within gynecological tumors has been well known for several decades. However, the prognostic role of their presence in various tumors is not yet understood as several scientific studies reveal contradictory information with both positive and negative correlation between the number of mast cells and tumor aggressiveness. In recent years, some authors reported that increased numbers of mast cell in the background of cervical and endometrial carcinomas are usually correlated with a worse prognosis when compared to similar histopathologic lesions with no mast cell microenvironment. On the other hand, similar studies regarding ovarian and breast carcinoma demonstrated strong positive correlation between increased mast cell numbers and favorable outcome. Therefore, we now have increasing evidence showing that mast cells tend to gather within and around neoplastic proliferations and could either promote or inhibit tumoral growth, based on regional stromal environment. In this article we aim to evaluate the mast cell microenvironment in smooth muscle tumors of the uterine corpus and attempt to establish their diagnostic implications and prognostic value.

Keywords: leiomyoma, mast cell microenvironment, smooth muscle tumors

INTRODUCTION

Leiomyoma is the most frequent neoplasm of the gynecological tract, affecting up to 40% of women during their reproductive years (1). It is a benign tumor with many histological variants, including but not limited to: mitotically active leiomyoma, leiomyoma with bizarre nuclei, leiomyoma with fumarate hydratase abnormality, cellular leiomyoma,

leiomyoma with hydropic change, apoplectic leiomyoma, epithelioid leiomyoma, myxoid leiomyoma and others (2,3). On top of this extremely heterogeneous histopathological spectrum and besides their less frequent malignant counterparts, leiomyomas also have many differential diagnoses, which may cause clinical and therapeutical concerns. Distinguishing between benign leiomyomas and their ma-

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lignant counterparts is often difficult, especially when they feature cytologic atypia, necrosis or an absolute increase in the number of mitotic figures (2,4,5). In the latest Classification of Female Genital Tumors, the World Health Organization has published well-defined histopathologic criteria for each variant, but in some cases the differential diagnosis may pose an important challenge for the pathologist (6,7). Several authors have proposed that the density of mast cells within this category of tumors can be used as an index for aggressiveness or malignancy.

MATERIALS AND METHODS

This is a retrospective unicentric study including a total of 328 cases from female patients diagnosed with smooth muscle tumors of the uterus between January 2019 and November 2021 in the Department of Pathology of the University Emergency Hospital Bucharest, Romania. Inclusion criteria for this study was represented by the histopathological diagnosis of a smooth muscle tumor of the uterine corpus on hysterectomy or myomectomy specimens. Exclusion criteria were diagnoses on curettage specimens, because the small sample size would not allow proper evaluation of mast cell count. All patients diagnosed during this period who met the inclusion criteria were added to this study. Besides these cases, an additional 22 non-fibromatous myometrial samples have also been included in the study. All patients included in this study expressed their written consent for participating via appendix nr. 4 to the methodological norm for the application of law nr. 104/2003 regarding the handling of human corpses and the removal of organs and tissues from corpses for transplantation from 01.04.2004, which is mandatory for accepting and processing histopathological specimens in any laboratory, according to Romanian law. This study has been approved by the Local Ethic Committee of the University Emergency Hospital Bucharest, Romania, with register number 751/08.12.2021.

In order to perform the histopathological examination, paraffin-embedded tissue samples from selected cases have been retrieved from the laboratory archive and fresh sections were cut at 3-5 μm . After dewaxing at 50°, the sections were rinsed and subsequently stained with hematoxylin and eosin. Before including in the study, each case was reviewed and reclassified according to the latest World Health Organization (WHO) classification of the female genital tumors. For each case, one paraffin block, including representative areas, was selected for histochemical staining with toluidine blue. Microscopic examination was performed using a Nikon Eclipse E600 microscope and photo-

graphs were taken using a LabCam microscope adaptor for iPhone 11 Pro Max. Intratumoral mast cells were counted on at least 25 consecutive high-power fields (HPF) and the average amount of mast cells per mm^2 was calculated for analysis. The results were subsequently correlated with the histopathological diagnosis, presence of atypia, necrosis and mitotic activity, using Microsoft Excel.

RESULTS

The mean age of the patients with smooth muscle tumors of the uterine corpus was 50.28 years, ranging from 31 to 67 years. The mean tumor diameter was 12 cm, ranging from 3 cm to 19 cm. The total number of mast cells identified varied from 0 to 156 per 10 HPF, with an average of 28 mast cells per 10 HPF in smooth muscle tumors and 3 mast cells per 10 HPF in normal myometrium. No significant changes in the number of mast cells were observed based on age or various phases of the menstrual cycle. Across the entire spectrum of smooth muscle tumors, the size of the lesion correlated best with a high number of mast cells. From all benign leiomyomas larger than 10 cm, 94,6% of had more than 30 mast cells / 10 HPF. Apoplectic leiomyomas had a mean of 48 mast cells / 10 HPF, with more than 70% of cases featuring at least 40 mast cells / 10 HPF. High numbers of mast cells were also observed in cellular leiomyomas and mitotically active leiomyomas. Less than 10 mast cells / 10 HPF were observed in epithelioid leiomyomas and in leiomyosarcoma. Cases with multiple leiomyomas larger than 10 cm had similar number of mast cells, the mean difference in the number of mast cells between synchronous leiomyomas being 7 mast cells/10 HPF. However, all the leiomyomas from the same patient, that measured more than 10 cm, featured more than 30 mast cells/10 HPF. Smaller leiomyomas from the same patients had either no mast cells or a lower number (mean 8 mast cells/10 HPF). No correlation has been observed between the presence of mast cells and other inflammatory cells (lymphocytes, plasma cells, eosinophils). None of the leiomyomas that were present in patients with endometrial neoplasms or hyperplasia (mean size 4 cm) featured a number of mast cells higher than 10 (mean number 3 mast cells/10 HPF). A notable difference has been observed between submucosal, intramural and subserosal leiomyomas, in regard to the number of mast cells. Intramural leiomyomas, larger than 10 cm, showed a significantly increased number of mast cells (mean number 88 mast cells/10 HPF), in comparison to the subserosal (mean number 36 mast cells/10 HPF) or submucosal leiomyomas (mean number 49 mast cells/10 HPF).

TABLE 1. Average number of mast cells per 10 HPF in smooth muscle tumors of the uterine corpus compared to normal myometrium

Type	Average number of mast cells / 10 HPF
Normal myometrium	3
Leiomyoma	
– mitotically active leiomyoma	43
– leiomyoma with bizarre nuclei	30
– leiomyoma with fumarate hydratase abnormality	22
– cellular leiomyoma	37
– leiomyoma with hydropic change	16
– apoplectic leiomyoma	48
– epithelioid leiomyoma	8
– myxoid leiomyoma	12
Leiomyosarcoma	9
Smooth muscle tumor of uncertain malignant potential (STUMP)	15

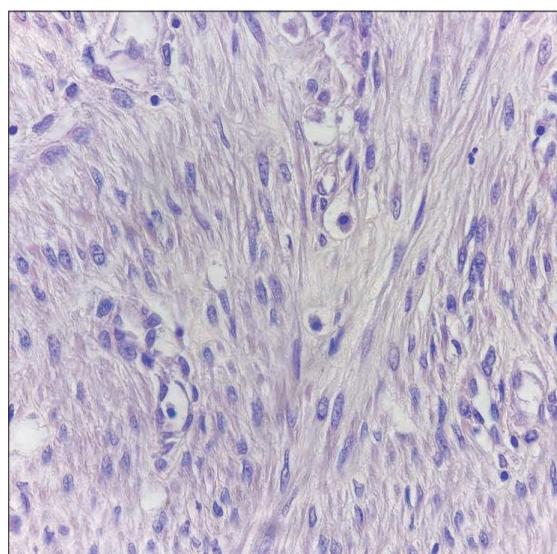


FIGURE 1. High magnification image showing scattered mast cells between the smooth muscle fibers of a typical leiomyoma (H.E. stain, 400x)

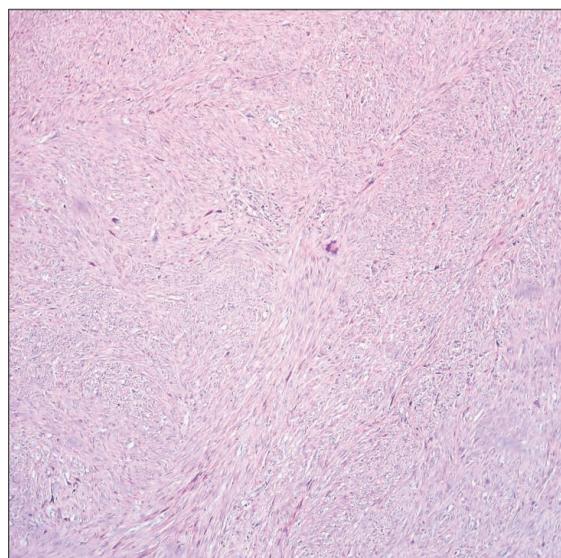


FIGURE 2. Medium-power field of a leiomyoma with bizarre nuclei (H.E. stain, 100x)

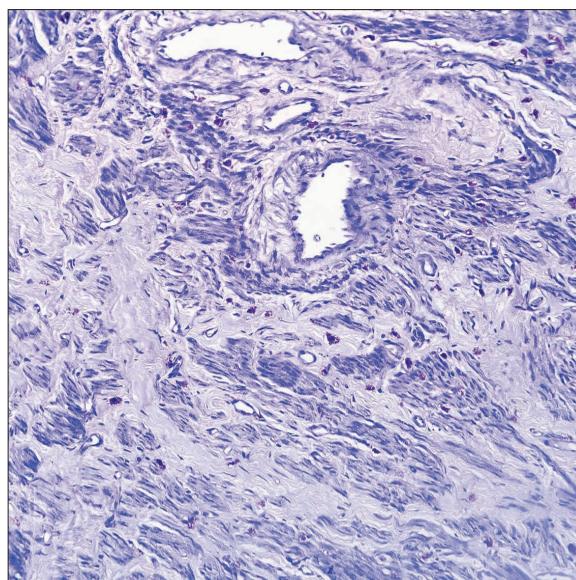


FIGURE 3. High-magnification field showing mast cells metachromatically stained with toluidin blue, with greater intensity in cells with smaller granules (Toluidin blue stain, 400x)

DISCUSSIONS

According to the latest World Health Organization Classification, smooth muscle tumors of the uterine corpus are classified into: leiomyoma, with its several histological subtypes, leiomyosarcoma and smooth muscle tumor of uncertain malignant potential (STUMP) (6,7). The latter includes tumors with morphological features that exceed histopathological criteria for leiomyoma, but are insufficient for a diagnosis of leiomyosarcoma and behave in a malignant fashion only in a minority of cases. Although benign, there are multiple histologic variants of leiomyoma with various microscopic, etiologic and clinical characteristics.

Approximately 40% of leiomyomas are associated with clonal cytogenetic aberrations. Most intravenous leiomyomatoses are characterized by a specific chromosomal aberration: der(14)t(12;14)(q15;q24) (8,9). These cases are also known to cause pulmonary or atrial metastases (10,11). Multiple skin and uterine leiomyomas can be associated with renal clear cell carcinoma in the context of renal carcinoma-leiomyomatosis syndrome, characterized by germline heterozygous loss-of-function mutation of fumarate hydratase gene, FH (1q43), which is not seen in sporadic leiomyoma (12,13). Additionally, Rico et al. has also reported the occurrence of a pheochromocytoma in a patient with the same mutation (14).

Uterine leiomyomas are usually asymptomatic. Patients may present with vaginal bleeding, or even anemia if menorrhagia or hypermenorrhea is severe (15). When present, acute abdominal symptoms are often secondary to rupture, torsion or in-

intratumoral hemorrhage, which may occur in apoplectic leiomyomas (15,16). Other presenting symptoms may be infertility, history of repeated abortions, abdominal swelling or pain (15,17). Treatment involves myomectomy, arterial embolization or simple hysterectomy, with excellent prognosis in all cases (15,18,19).

Upon gross examination, leiomyomas are more frequently multiple and/or multinodular rather than solitary. They are usually well-circumscribed, unencapsulated, with bulging, white to tan and whorled cut surface (20,21). Their size may range from a few millimeters to several centimeters. Red degenerative areas with “beefy” appearance may be seen due to infarction and secondary hemorrhage, if the patient is pregnant or on oral contraceptives (2,21)

Discrete foci of hemorrhage or ischemic necrosis can also be present. Subserosal pedunculated tumors tend to torsion and detach, forming so-called parasitic leiomyomas (2,3). Other particular gross aspects may occur in various leiomyoma subtypes. Highly cellular leiomyoma is often tan to yellow and has a soft cut surface (22-25). Apoplectic/hemorrhagic leiomyoma may show stellate hemorrhagic areas and cystic change (26,27). Epithelioid leiomyoma tends to have soft, tan cut surface, while myxoid leiomyoma usually has a gelatinous, soft and gray cut surface (28,29). Epithelioid leiomyomas have also been observed in patients with tuberos scleriosis and rheumatoid arthritis (29). Lipoleiomyoma shows alternating yellow and white areas (30–32). Diffuse leiomyomatosis is characterized by diffuse, regular thickening of the uterine wall due to multiple and confluent small leiomyomas (33). Intravenous leiomyomatosis presents as multiple worm-like plugs of white to slightly pink or tan tissue, filling and distending the myometrium (8-10).

Microscopically, leiomyomas are composed of intersecting fascicles of spindle cells with variable collagen deposition (34). Each particular variant of benign leiomyoma has characteristic histologic findings, such as increased cellularity, increased mitotic activity, large multinucleated nuclei, staghorn vessels or even areas of hemorrhage and necrosis (2,3,28). Regardless of the histologic variant, variable numbers of mast cells may be encountered when examining the pathologic samples (35). Multiple authors have studied the incidence of mast cells within ordinary leiomyomas and normal myometrium, reporting somewhat contradictory data (36). Zhu et al. has attributed the presence of mast cells in uterine smooth muscle tumors to the expressions of chemokines CCL5 and CCL11 (37). Other authors have reported that the mast cells are recruited through RANTES and Eotaxin secretion (38).

Leiomyosarcomas are solitary, usually large masses, with variably circumscribed margins (2).

When associated with other uterine smooth muscle tumors, they typically represent the largest mass. Upon sectioning, they reveal a soft, fleshy, bulging and white-gray cut surface. Epithelioid morphology is associated with softer consistency and myxoid morphology, with gelatinous areas. Necrosis, hemorrhage or cyst formation may be seen (2,3,28).

The microscopic aspect of leiomyosarcoma and its diagnostic criteria varies considerably, based on histologic subtype. Tumor cells can be spindle, with perinuclear vacuoles, brisk mitotic activity and variable degrees of cytologic atypia, arranged in long intersecting fascicles or polygonal-shaped, with round nuclei and ample eosinophilic or clear cytoplasm, forming diffuse, nested, corded or plexiform growths (2-4). Myxoid pattern is composed of spindle to stellate cells with scant eosinophilic cytoplasm, arranged in diffuse or fascicular growths with frequent hypocellular areas and highly variable cytologic atypia and proliferative activity (4,39). Admixture of histologic subtypes is not infrequent and dedifferentiation may occur (2,40).

Mast cells are broadly present in all human tissues. They have also been observed in various types of tumors and in many cases, they appear to have clinical significance. For example, mast cell count has been demonstrated to be negatively correlated with the development of colonic cancer (41). Moreover, patients diagnosed with various subtypes of soft tissue sarcomas which feature high numbers of mast cells appear to have improved outcome and better overall 5-year survival rates (42). Distinguishing between neurofibroma and schwannoma may sometimes be difficult, but counting mast cells may aid in the differential diagnosis (43).

Maluf et al. reported benign leiomyomas with more than 10 mast cells / HPF (36). Most of the time, the surrounding myometrium does not reveal a similar increase in mast cells (44). Ribatti et al. also reported an increased number of tryptase-positive mast cells and a considerably greater microvasculature density in leiomyomas compared to myometrial tissue (45). Rudolph et al. has observed that the mediators secreted by the mast cells (histamine and serotonin) seem to be implicated in the strong contraction of the myometrium (46,47). Based on their findings, angiogenesis in smooth muscle tumors of the gynecological tract appears to be highly correlated with tryptase and leptin-positive mast cell counts (45).

Yavuz et al. reported that atypical leiomyomas feature an increased mast cell count in comparison to leiomyosarcomas and concluded that their density can be used in the differential diagnosis of these two entities (48). Orii et al. studied intratumoral mast cell density in various smooth muscle tumors of the uterine corpus using toluidine blue staining and tryptase immunostaining and concluded that

atypical and cellular leiomyomas feature higher amounts of mast cells than leiomyosarcoma and ordinary leiomyoma (49,50). They also suggested that mast cell count might aid the pathologist in the differential diagnosis between smooth muscle tumors of the uterine corpus (38,47). Another interesting finding is that mast cells appear to be significantly lower in high stage tumors compared to early-stage tumors, but no significant correlation was noted between overall survival and mast cell count (49).

Zhu et al. also discovered that leiomyosarcoma and typical leiomyoma usually feature extremely lower amounts of mast cells in comparison to cellular leiomyoma (37,50).

Leiomyomas are frequently therapeutically managed with gonadotropin-releasing hormone agonists (GnRH-a) in order to reduce tumor volume. Nakayama et al. (51) published a study including uterine leiomyomas from patients treated with GnRH-a and untreated groups, showing that GnRH-a treated leiomyomas show increased number of mast cells. It has also been hypothesized that in-

creased numbers of intratumoral mast cells in uterine leiomyomas may play a significant role in GnRH-a treatment resistance, due to their ability to produce insulin-like growth factor-I without the participation of ovarian steroid hormones (52).

CONCLUSIONS

Additional to the absence of necrosis and mitoses, the increased number of mast cells encountered in large leiomyomas, apoplectic and cellular leiomyomas can serve as a reassuring criterion, aiding in the differential diagnosis with leiomyosarcoma. Our study is in concordance with the current scientific literature, which has also observed a lack of mast cells in leiomyosarcomas. Ordinary leiomyomas feature a low number of mast cells, 76% of them having less than 10 mast cells / 10 HPF. This observation should be urged pathologist to pay close attention to the morphology and to the microenvironment of smooth muscle neoplasms, in order to avoid making an erroneous diagnosis.

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