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Uterine Mesenchymal Tumors: One year Institutional experience in a Tertiary Care Centre in South India

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Abstract
Background Uterine mesenchymal tumors have been conventionally classified into two broad categories; Smooth Muscle Tumors (SMT) and Endometrial Stromal Tumors (EST). Most common being Smooth muscle tumors, its accurate categorization by light microscopic examination is important and at times can be challenging. Here we discuss Institutional experience of Uterine mesenchymal tumors for 1 year in a tertiary care centre in South India.
Aim To determine the various histomorphological types of Uterine Mesenchymal Tumors and to study its correlation with Clinico-Pathological findings.
Materials and Methods It is a descriptive record based study. Study was carried out in a tertiary care centre in South India. All the consecutive hysterectomy and myomectomy cases received in the department of Pathology were studied. Cases from women aged between 20-80 years, received from January 2019 to December 2019 and diagnosed as mesenchymal tumors of the uterus were retrieved and reviewed.
Results In our study period of 12 months, a total of 246 cases were noted. There were 212 Hysterectomy specimens and 34 Myomectomy specimens. Average size of the lesions was 4.9 cm and average age at presentation was 45yrs. Benign tumors were more common compared to malignant tumors. Out of total number of 246 cases, 243 were Leiomyoma and its variants. Typical leiomyoma were 179 cases and variants included Leiomyoma with hyaline change 34 cases, which was commonest followed by adenomyoma 11 cases, cellular leiomyoma 8 cases, leiomyoma with myxoid change 4 cases, lipoleiomyoma 2 cases, atypical leiomyoma 2 cases and leiomyoma with red degeneration and leiomyoma with amianthoid fibers 1 case each. Among malignant tumors 1 case was Leiomyosarcoma (LMS) and 2 were Endometrial Stromal Sarcoma (ESS).
Conclusion It is important to differentiate benign and malignant mesenchymal tumors due to differences in their clinical outcome. Most common being Smooth muscle tumors, its accurate categorization by light microscopic examination is important and at times can be challenging. Role of surgical pathologist in making this distinction, especially in difficult cases cannot be underestimated. Although Immunohistochemical stains are helpful in establishing the final diagnosis, the morphologic features are superior to all the other ancillary techniques for this group of neoplasms. Recent application of molecular techniques has identified numerous lesions with distinctive genetic abnormalities and clinicopathological characteristics.

Keywords: Mesenchymal Tumor of Uterus, Leiomyoma, Leiomyosarcoma, Endometrial Stromal Tumor

Introduction
Uterine mesenchymal tumors are the most common and heterogeneous group of neoplasm. The separation of uterine smooth muscle neoplasms into prognostically and therapeutically useful categories may at times be difficult. Assessment of nuclear atypia is subjective whereas counting mitoses would appear to be an entirely objective procedure. Many factors, including interpretative variation between pathologists, can affect the final mitotic counts. Majority of these tumors show homologous mesodermal tissue differentiation. However, on occasions, it is not uncommon to see heterologous differentiation with elements like cartilage, skeletal muscle and bone [1, 2]. Mitotic count, atypia, and coagulative necrosis are the main histologic criteria that define leiomyosarcoma. Determining the type of necrosis can be very challenging when key histologic features of ischemic-type necrosis are often absent. Ancillary stains including p16, p53, MIB-1, trichrome, and reticulin may be helpful in tumors harboring necrosis in difficult cases.

The spectrum of mesenchymal tumors of uterus has expanded recently, identification of prevalent, recurrent molecular alterations has led to new classification of endometrial stromal tumors. Diagnostic criteria of several rare and miscellaneous tumor types have been refined**.** The new definition of high-grade endometrial stromal sarcoma disregards the number of mitotic figures as a primary diagnostic criterion and instead specifies moderate atypia still resembling stromal origin but lacking the pleomorphism of undifferentiated uterine sarcoma; these tumors also harbor a JAZF1-SUZ12 gene rearrangement [3, 4].
Pathologist role is very crucial in making this distinction, especially in difficult cases. Although Immunohistochemical stains are supportive towards establishing a final diagnosis, to identify morphologic features is utmost important in diagnosing these cases. Here we discuss uterine mesenchymal tumor encountered in one year period at our Institute [5].

Material and Methods

Hospital based study was performed in the Department of Pathology at Father Muller Medical College Hospital, a tertiary care center in South India. Ethical clearance for the study was obtained before start of the study from Ethical Committee. All consecutive cases of Hysterectomy and Myomectomy cases for the study period of 12months were included. Specimens from all age group were studied. Initially specimens that were received in 10% buffered formalin were looked for the presence of tumor location grossly and cut surface is noted. Grossed and representative section are given, further processed in automatic tissue processor, sectioned and stained with Hematoxylin and Eosin. All the slides prepared by above described procedure were retrieved and reviewed. Immunohistochemistry slides were also retrieved and reviewed for cases where it was performed. Epithelial tumors of Uterine Corpus, metastatic tumors and cases treated with neoadjuvant chemotherapy were excluded. The histopathological evaluation was performed and the final diagnosis of the tumor type and subtype were made according to WHO (World health organization) 2014 classification. Malignant tumors were reported in accordance with TNM Pathological staging, AJCC 8th Edition. For all the cases clinical details with regard to age, presenting symptoms, last menstrual period, ultrasound finding, obstretic history were collected from hospital medical records. For statistical analysis, the data was entered in MS excel and descriptive statistics were performed.

Results

In our study period of 12 months, a total of 246 cases were retrieved and reviewed. There were 212 Hysterectomy specimens and 34 Myomectomy specimens (Fig 1). Benign tumors were more common in comparison with malignant tumor (Fig 2). Patients were from 20-80yrs of age and average age at presentation was 45yrs (Fig 3). Average size of the tumor was 4.9 cm. Out of total number of 246 cases, 243 were Leiomyoma and its variants (Table 1& Figure 4). Typical leiomyoma were 179 cases and variants included Leiomyoma with hyaline change 34 cases, which was commonest followed by adenomyoma 11 cases, cellular leiomyoma 8 cases, leiomyoma with myxoid change 4 cases, lipoleiomyoma 2 cases, atypical leiomyoma 2 cases and leiomyoma with red degeneration and leiomyoma with amianthoid fibers 1 case each. Among malignant mesenchymal tumors of uterus 1case was of Leiomyosarcoma (LMS) and 2 cases were of Endometrial stromal sarcoma (ESS) (Table 2 &Fig 5). Grossly typical leiomyoma were graywhite with whorled cut surface. Tumor with red degeneration showed beefy cut surface. We also encountered a pedunculated submucosal fibroid, presenting as cervical polyp. The case of Leiomyosarcoma showed variegated appearance with graywhite, necrotic and haemorrhagic areas. In 2 cases of Endometrial stromal sarcoma, presented as nodules in the the myometrium (Fig 6 a, b). Microcopically there were two unusual variants of Leiomyoma that is Leiomyoma with Amianthoid fibres and Lipoleiomyoma. Amianthus is type of asbestos with fibers.Tumor shows thick collagen fibers resembling amianthus hence called Amianthoid Leiomyoma. Case of Leiomyosarcoma showed tumor necrosis with marked atypia and increase count of abnormal mitosis. Endometrial Stromal sarcoma showed infiltrative tumor resembling proliferative endometrium and showed CD 10 positivity on IHC (Fig 6 c, d).

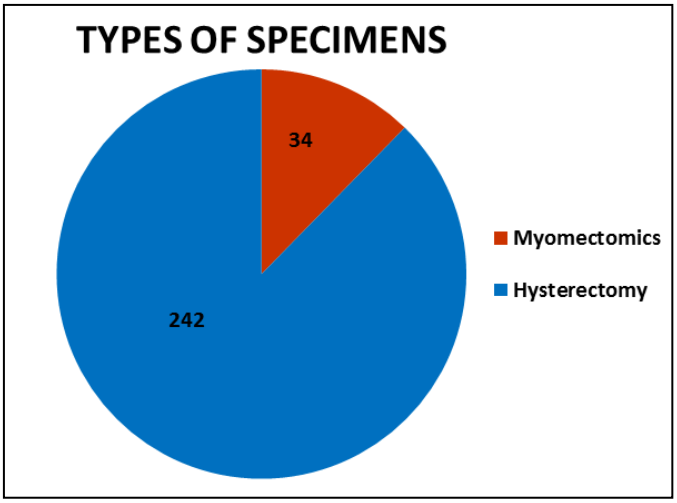

Fig 1: Types of Specimens

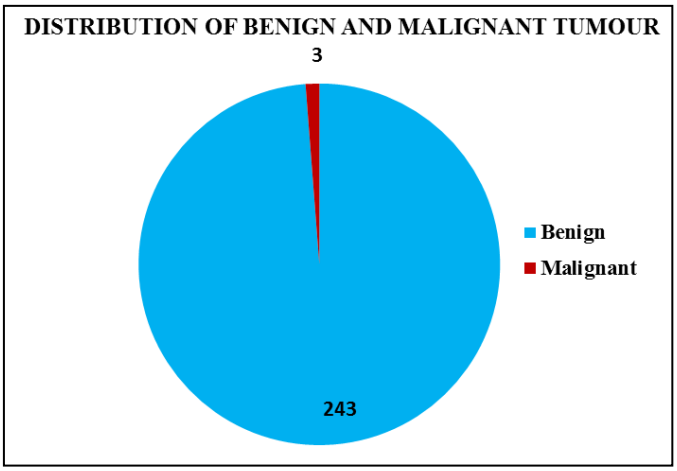

Fig 2: Distribution of Benign and Malignant Tumor

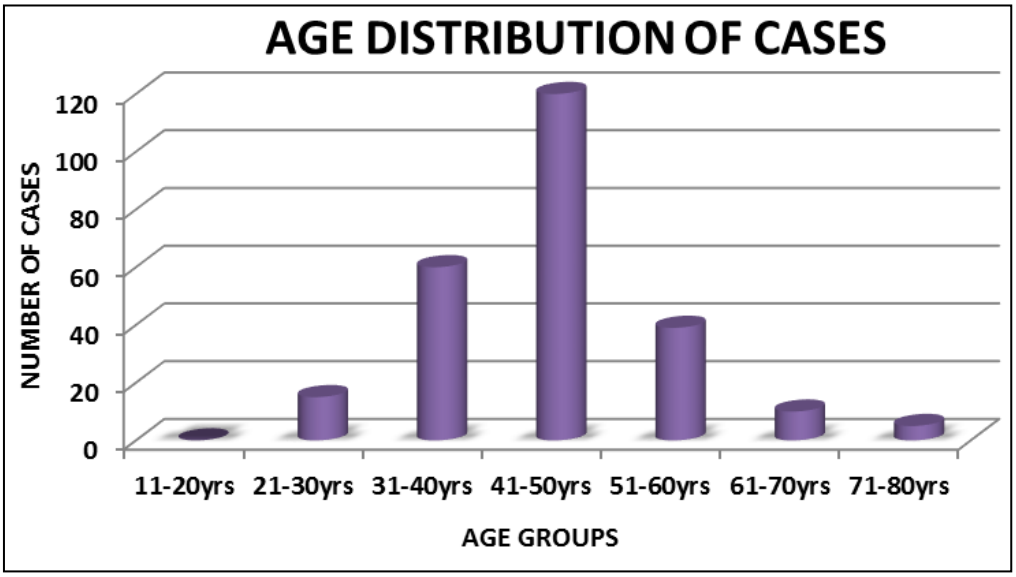

Fig 3: Age distribution of cases

Table 1: Types and frequency of Benign lesions (variants of leiomyoma)

Types of Leiomyoma	No. of cases	Percentage
Typical leiomyoma	179	**79%**
Leiomyoma with hyalinisation	34	**14%**
Leiomyoma with adenomyosis	11	**4%**
Cellular leionyoma	8	**3%**
Leiomyoma with myxoid change	4	**1.6%**
Lipo –leiomyoma	2	**0.8%**
Atypical leiomyoma	2	**0.8%**
Leiomyoma with red degeneration	1	**0.4%**
Leiomyoma with Amianthoid like fiber	1	**0.4%**
Total	**243**	**100%**

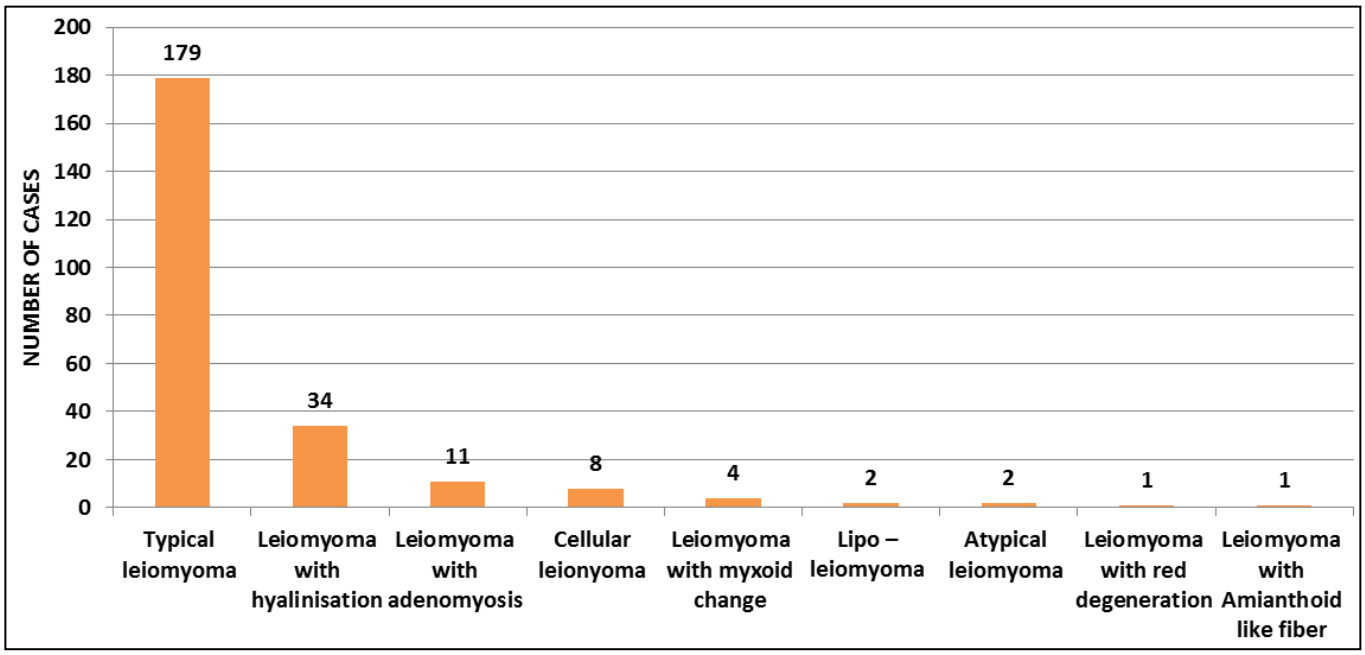

Fig 4: Types and frequency of Benign lesions (variants of leiomyoma)

Table 2: Type and frequency of Malignant lesions

Lesions	No. of cases	Percentage
Leiomyosarcoma	1	33.4%
Endometrial stromal sarcoma	2	66.6%
Total	3	100%

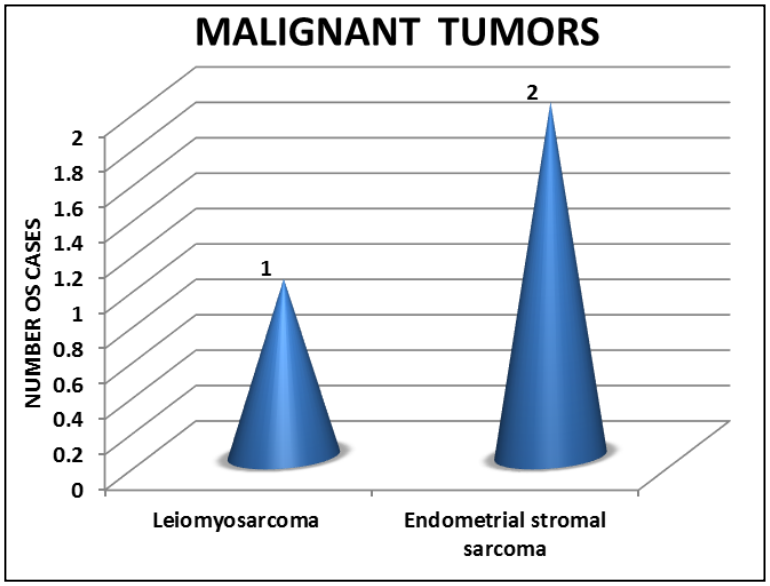

Fig 5: Type and frequency of malignant lesions

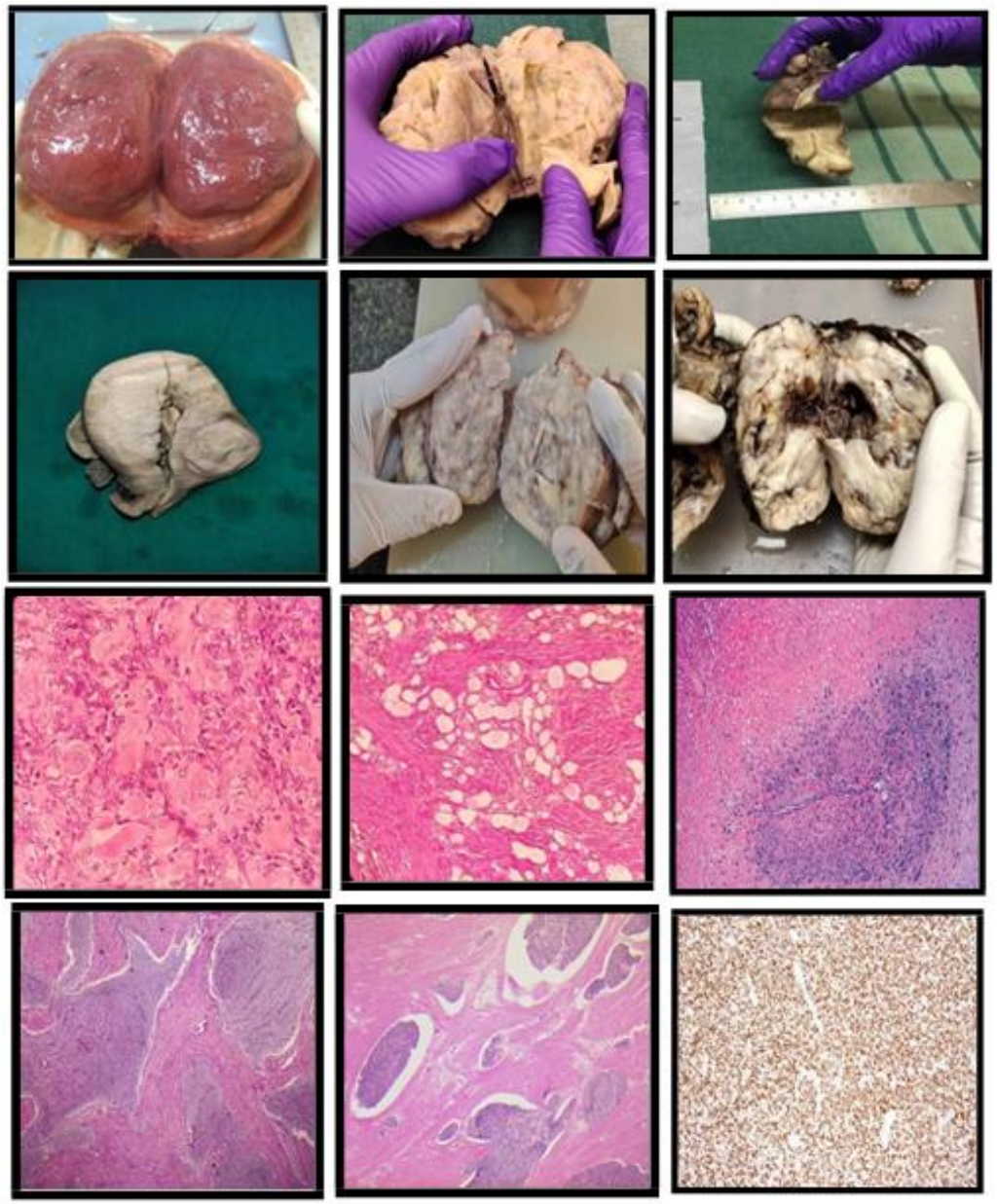

Fig 6: (Gross and Microcopy)

6a. First row: Leiomyoma with red degeneration, Leiomyoma with myxoid change and Pedunculated submucosal leiomyoma (from left to right)
6b. Second row: Endometrial stromal sarcoma case 1, Endometrial stromal sarcoma case 2, Leiomyosarcoma (from left to right)
6c. Third row: Leiomyoma with Amanthoid fibers, Lipoleiomyoma and Leiomyosarcoma (from left to right)
6d. Fourth row: Endometrial stromal tumor case 1, Endometrial stromal tumor case 2, IH: CD10 Positive (from left to right)

Discussion

The most common uterine tumor in the reproductive age group is Leiomyoma and are found in about 80% of all hysterectomy specimens. They may have a diverse clinical, radiological and morphological pattern. Clinically they may be sporadic or syndromic and may present with abdominal pain, menorrhagia and pelvic mass. Submucosal leiomyomas tend to present with abnormal uterine bleeding as well as prolapse into the vagina, as seen in our study in which case they should be differentiated from cervical and endometrial polyps, carcinoma and sarcoma.

In our study, majority of cases were benign tumors accounting upto 98.8% and malignant tumors were 1.2%. Among total specimens received, 86.1% were hysterectomy and 13.9% were myomectomy making hysterectomy a most common procedure performed especially for benign smooth muscle tumors followed by myomectomy. Similar findings were noted in many other studies. In a study by Manjula K [6] *et al.*, of the total 12,285 surgical specimens received for histopathological examination in the department during the study period, 1,832 were hysterectomies and 13 were myomectomy specimens [6, 7]. In a study by Bindu Vijaya Kumar [8] *et al.*, hysterectomy was done in 58.9%, and myomectomy were performed in 41.4% [9]. In a study by Budihal [10] *et al.*, among 12,285 surgical specimens received for histopathological examination during the study period, 1914 were hysterectomies, 25 were myomectomies, 3 were debulking specimens and one was polypectomy specimen [10, 11]. In a study by Jinu Abraham [12] *et al.*, there were 710 hysterectomy and 27 myomectomy specimens that were studied [12, 13].

The age at presentation was between 20-80 years with mean age being 45years. This finding was similar to majority of the studies. In a study by Bindu Vijay Kumar *et al.*, mean age was 41.9 years(SD 9yrs), Kempula Deepamal [14] *et al.*, leiomyomas occurred mostly in women aged 31-50 years (90.23%), Bhatta Sushma [15] *et al.*, uterine leiomyoma were most common in the age group of 41-50 years (54.76%). In a study by Jinu Abraham *et al.*, age of patients ranged from 20 years to 72 years with peak incidence in the 4th decade. Most common presenting complaint in our study was abnormal uterine bleeding followed by mass per abdomen and pain abdomen. In a study by Seema Dayal [16] *et al.*, the chief clinical features were menorrhagia in 55.6%, metrorrhagia in 16.7%, and polymenorrhagia 5.5%, the other presenting symptoms were abdominal mass 22.2% followed by abdominal pain 21.1% and others 1.1%.

In a study by Bindu Vijaya Kumar *et al.*, the most common presenting symptom was abnormal uterine bleeding in 53.5% of cases. In our study majority of cases were benign tumors accounting to 98.8% and malignant tumors were 1.2%. Similar was noted in a study by Budihal *et al.*, leiomyoma was the most common tumor accounting to 96.95% of all the tumours. In the study 98.11% cases showed features of conventional leiomyoma and 8 cases showed variants of leiomyomas 1.68%. Of these, 4 cases were lipoleiomyoma, 2 atypical leiomyoma, one cellular leiomyoma and one apoplectic leiomyoma.

In a study by Bindu Vijay Kumar *et al.*, prevalence of fibroid variants was 1.8% and there was one case of LMS in this cohort (0.03%). Of total leiomyoma variants, 60% were cellular leiomyoma, 19.6% were mitotically active leiomyomas (MAL),14.3% were leiomyomas with bizarre nuclei (LBN), and 5.4% cases were reported as smooth muscle tumour of uncertain malignant potential (STUMP). WHO enlists the histopathological variants of leiomyomas and various usual and unusual variants as described in the literature. In a study by Manjula K *et al.*, benign tumors were diagnosed in 95.45% showed features of usual leiomyoma, malignant tumor of the myometrium was diagnosed in 0.054%. Variants of leiomyoma included myxoid leiomyoma, lipoleiomyomas, hemorrhagic cellular leiomyoma, one case each of cellular, epithelioid, bizarre, neurilemoma type and leiomyomas with lymphocytic infiltration.

In a study by Jinu Abraham *et al.*, secondary changes were observed in 24.2% cases and histological variants comprised 7.5% of the cases. In their study histological variants which posed diagnostic difficulties were cellular leiomyomas, atypical leiomyoma, epithelioid leiomyoma, and leiomyomas with secondary changes including haemorrhagic infarction, myxoid change and perinodular hydropic change.

The difficulty of predicting the biological behavior of uterine smooth muscle tumors has been recognized for many years. While the vast majority of these neoplasms will follow an entirely benign course, a small but significant minority will behave aggressively, exemplified by metastatic disease or recurrence. The central clinical purpose of histopathologic classification and grading of neoplasms is to estimate prognosis, including the likelihood for the development of local relapse or metastasis. To achieve this aim, a set of morphologic features that reliably predict clinical recurrence or metastasis is required.

The 2014 World Health Organization classification of Female Reproductive Organ has updated its criteria for mesenchymal tumors of the female reproductive tract and variants of benign smooth muscle tumors are diagnosed according to their unusual histologic features. Increased cellularity, higher than that of nearby myometrium, is seen in a cellular leiomyoma, and at times, a cellular leiomyoma may have short spindle cells resembling an endometrial stromal tumor. Leiomyomawith bizarre nuclei (also called atypical, symplastic and pleomorphic) show the presenceof scattered large atypical cells

Smooth muscle tumors (SMTs) and Endometrial stromal tumors (ESTs) are the most common mesenchymal tumors of the uterus. Mesenchymal tumors of the uterus comprise of a heterogeneous group which may pose diagnostic challenges. Smooth muscle and Endometrial Stromal Tumors constitute the majority of the group and 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. Although Immunohistochemical stains are supportive towards establishing a final diagnosis, morphologic features is utmost important in diagnosing these cases. Immunohistochemistry markers are helful in unusal cases Spectrum of differentiation patterns in low-grade stromal sarcoma has been extended. As well as sex-cord-like areas, rhabdoid and retiform differentiation have recently been described. True glands and tubules are well described and it seems likely that most examples of aggressive endometriosis represent low-grade stromal sarcoma with extensive endometriold glandular differentiation. It is common for stromal tumors to show areas of smooth muscle differentiation. Those where more than 30% of the tumor was made up of the lesser element (sometimes called stromomyomas) have recently been the subject of a study which suggests that they should be reported as endometrial stromal nodules or low-grade stromal sarcomas with smooth muscle differentiation, as the one tumor of seven with follow-up that recurred, did so as a pure lowgrade stromal sarcoma.

Although their diagnosis is straight forward in most cases, difficulties arise with particular leiomyoma variants, in a highly cellular leiomyoma that can be confused with an Endometrial stromal tumor and Leiomyoma with bizarre nuclei and mitotically active leiomyoma where one has to rule out Leiomyosarcoma. There has been multiple classification schemes proposed to emphasize on mitotic rate, nuclear atypia and the presence or absence of necrosis. Smooth muscle tumors arising within the myometrium are either frankly malignant with nuclear atypia, a high mitotic count and necrosis or are clearly benign with bland nuclear features with low or no mitotic count. Most challenging ones are the group of smooth muscle tumors with intermediate degree of mitotic activity and nuclear atypia.

Conclusion

Majority of the uterine SMTs are readily classifiable as benign or malignant based on their gross and microscopic appearances. However, when unusual features are seen in some leiomyoma variants, the differential diagnosis with a leiomyosarcoma may become challenging. Moreover, diagnostic criteria for the different subtypes of leiomyosarcoma are not uniform. Non smooth muscle tumors that originate in the uterus may show overlapping histologic and even immunohistochemical features with uterine SMTs, more commonly with the spindle and epithelioid variants, complicating their correct classification. A panel of antibodies rather than a single antibody should be used when the differential diagnosis is between U-SMTs and their mimics.The diagnosis of malignant uterine SMTs has important prognostic and therapeutic implications. Recent application of molecular techniques has identified numerous lesions with distinctive genetic abnormalities and clinicopathological characteristics.

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