ORIGINAL ARTICLE

Histomorphological Spectrum of Uterine Smooth Muscle Tumors

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Abstract

Introduction: Uterine smooth muscle tumors are the most common tumors of female genital tract and among these leiomyomas predominate. Leiomyomas most commonly occur during the reproductive years in women with manifestation of abnormal uterine bleeding and abdominal pain. These exhibit wide range of morphological variants and secondary changes. Here, we present a study of 70 cases, which includes rare variants and degenerative changes in leiomyomas.

Materials and methods: A retrospective study conducted in a department of pathology for a period of 1 year from January 2019 to December 2019 at a tertiary care hospital. Seventy patients were diagnosed as leiomyoma on histopathological examination of 124 hysterectomy specimens and one myomectomy specimen and included in the study. Detailed microanatomic features were studied and recorded.

Result: Uterine leiomyoma was most common among the age-group of 41–50 years of age (64.21%). Most common location was intramural (54.29%). Secondary changes were observed in 48 cases (68.57%). Most common secondary change was hyaline degeneration noted in 38 cases (79.17%). Classical variant of leiomyoma was seen in 66 cases (94.28%) followed by one case (1.43%) each of symplastic, neurilemmoma-like, lymphocyte-rich, and cellular leiomyoma and leiomyomas with rare secondary changes like osseous and chondroid metaplasia.

Conclusion: Uterine smooth muscle tumors are commonly seen in perimenopausal females. Leiomyoma is associated with various pathologies comprising of degenerative changes and rare variants which sometimes can be misdiagnosed as malignancy. Hence, a vigilant histopathological examination is necessary to identify the various spectrum of uterine leiomyomas and associated pathologies.

Keywords: Degenerative changes, Osseous metaplasia, Parasitic, Uterine leiomyomas.

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Introduction

Uterine smooth muscle tumors are the most common tumors of female genital tract and among these leiomyomas predominate. These exhibit wide range of morphological variants and secondary changes due to unopposed estrogen stimulation.[1] Approximately 30–50% of women of reproductive age are affected by leiomyomas.[2] These tumors present with manifestations like abnormal uterine bleeding, abdominal pain, and abdominal lump.[3] These constitute a major cause of hysterectomy all over the globe, followed by adenomyosis, leiomyosarcoma, endometrial stromal tumors, secondary tumors, and vascular lesion.[4]

Histopathological features of leiomyoma show great variability with respect to clinical presentation, site, number, and presence of degenerative changes and rare variants. Even though the diagnosis of the leiomyoma is straightforward, few leiomyomas presenting with unusual histomorphological variant and rare secondary change may be confused with leiomyosarcoma or other endometrial lesions and arose a diagnostic difficulty.

Current study targeted to find out the histopathological spectrum of uterine smooth muscle tumors with special emphasis on degenerative changes and rare variants of uterine leiomyomas.

Materials and Methods

A 1-year retrospective study conducted in the department of pathology from January 2019 to December 2019 at a tertiary care hospital. During this study duration, 124 hysterectomy and one myomectomy specimens were received, among which 70 cases were of leiomyomas that were included in the study. The material was obtained from the patients admitted at the tertiary care hospital.

Relevant clinical history and ultrasonographic findings were recorded from patient's case paper. The specimens in 10% formalin were received along with a requisition form for the histopathological examination. A detailed gross examination including size, shape, location, consistency, and external surface was done.

The tissue bits from representative areas were taken for histopathological examination and were processed with routine procedures followed by paraffin blocks preparation. Multiple sections of five microns thickness were cut and stained with hematoxylin and eosin stain.

Detailed microscopic examination including type of histomorphological variant of leiomyoma, presence of secondary changes along with analysis of increased cellularity, nuclear atypia,

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presence of mitoses (per 10 HPF), crowding, overlapping of nuclei, and coagulative necrosis was done.

Result

During the 1-year study period, we received a total of 125 specimens (included 124 hysterectomy and one myomectomy). Out of which 70 cases (56%) were of leiomyoma.

Age of the patients ranged from 20 to 72 years with peak incidence in the fourth decade. Majority of the patients, i.e. 45 cases (64.29%) were between age-group of 41 and 50 years (Table 1).

In present study, majority of the patients were presented with menorrhagia as predominant presenting complaint, which constituted 34 cases (48.58%), followed by abdominal pain in 22 cases (31.43%) (Fig. 1).

Majority of the leiomyomas were intramural in location seen in 38 cases (54.29%) followed by seven cases (10%) of submucosal, three cases (4.28%) of subserosal leiomyoma, and one case of parasitic leiomyoma (1.43%).

In this present study of 70 cases, secondary changes were observed in 48 cases (68.57%) (Table 2). Among these, 38 cases (79.17%) had hyaline degenerative change and constituted commonest degenerative change observed in this study (Fig. 2). Five cases (10.41%) of leiomyoma were found to have calcific degeneration followed by one case (2.08%) each of red degeneration, myxoid degeneration, and cystic degeneration. There were two (4.16%) cases of leiomyoma showing heterologous differentiation in the form of osseous metaplasia (one case) and cartilaginous metaplasia (one case).

In the present study of 70 cases, the classical morphology or conventional variant of leiomyoma was noted in 66 cases (94.28%)

Table 1: Age-wise distribution of leiomyoma

Age-group	*Number of cases*	*Percentage*
<20 years	1	1.42%
21–30 years	4	5.71%
31–40 years	7	10%
41–50 years	45	64.29%
>51 years	13	18.58%
Total ($n = 70$)	70	100%

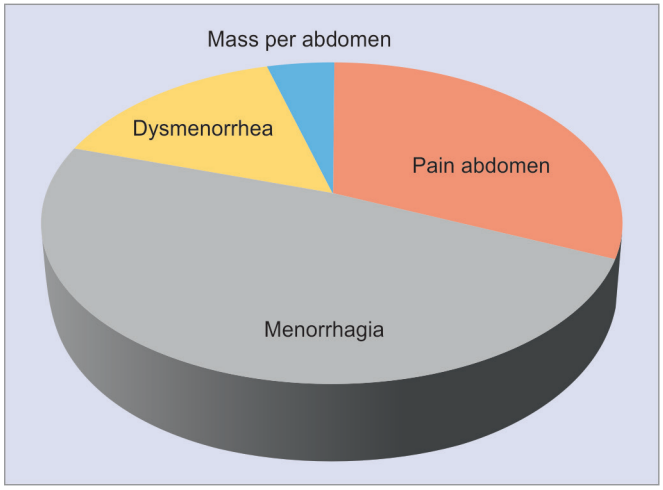


Fig. 1: Distribution of cases based on clinical symptoms

Table 2: Distribution of cases based on secondary changes

Secondary changes in leiomyoma	*Number of cases*	*Percentage*
Hyaline	38	79.17%
Calcification	5	10.41%
Red degeneration	1	2.08%
Myxoid degeneration	1	2.08%
Cartilaginous metaplasia	1	2.08%
Osseous metaplasia	1	2.08%
Cystic change	1	2.08%
Total ($n = 70$)	48	68.57%

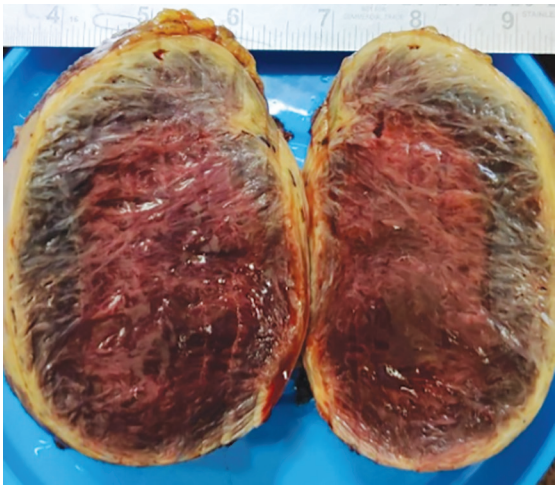


Fig. 2: Cut surface of leiomyoma showing red degeneration

Table 3: Distribution of cases based on variants

Leiomyoma variant	*Number of cases*	*Percentage*
Conventional	66	94.28%
Symplastic	1	1.43%
Neurilemmoma-like	1	1.43%
Lymphocyte-rich	1	1.43%
Cellular	1	1.43%
Epithelioid	Nil	Nil
Lipoleiomyoma	Nil	Nil
Mitotically active	Nil	Nil

(Table 3). Among the remaining four cases, one case each of neurilemmoma-like (1.43%), lymphocyte-rich (1.43%), symplastic (1.43%), and cellular leiomyoma (1.43%) were observed.

Discussion

Smooth muscle tumors are the most common among all the mesenchymal tumors of the uterus. These tumors may be an incidental finding in uteri removed for any other reasons, but they are also frequently responsible for a variety of common gynecologic and obstetric difficulties. Histologically, leiomyomas are easily identified as having a smooth muscle phenotype and being benign. Leiomyosarcoma constitutes a small percentage of uterine smooth muscle neoplasms and is highly malignant neoplasms diagnosed using modern diagnostic criteria. Most leiomyosarcomas are easily recognized both as showing smooth muscle differentiation and as malignant. A small number of uterine smooth muscle proliferations

pose a diagnostic difficulty for a variety of reasons involving either rare histomorphological characteristics or problems of phenotype or anticipated clinical behavior (benign or malignant or something in between).[5]

Leiomyomas are associated with several different recurrent chromosomal abnormalities, including rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas. Mutations in the *MED12* gene, which encodes a component of the RNA polymerase transcription complex, have been identified in up to 70% of leiomyomas. Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas; conversely, these tumors shrink postmenopausally.[1]

The age-group of the patients ranged from 19 to 68 years in the present study, and majority of the patients were in the range of 41–50 years (64.29%), which was consistent with studies done by Geethamala et al.[6] and Bhatta et al.[7] (54.76%).

Present study showed menorrhagia and abdominal pain were the predominant presenting chief complaints of the patients accounted 48.58 and 38.43%, respectively. This finding was consistent with the studies done by Geethamala et al.[6] and Kakulapati et al.[8]

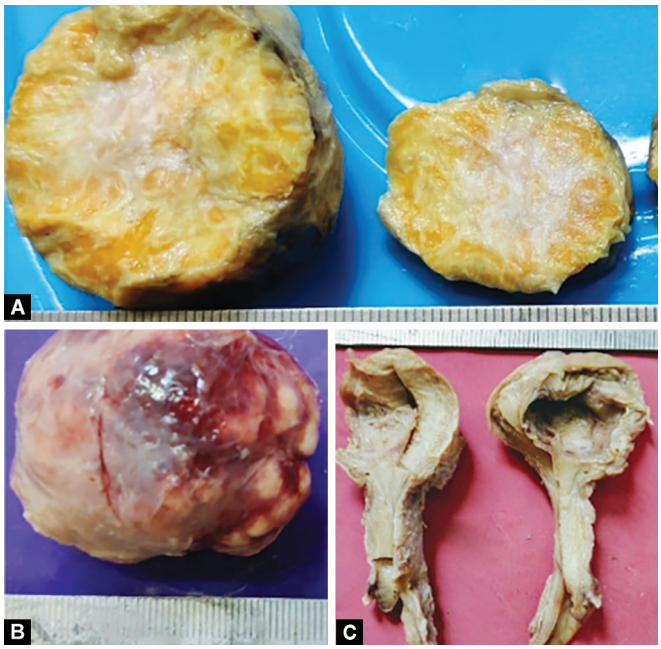
Most common location of leiomyoma was intramural (54.29%) followed by submucosal (10%). This observation was analogous to the study done by Geethamala et al.[6] and Naz et al.[9]

In the present study, degenerative changes were observed in 48 cases of leiomyoma (68.57%). Hyaline degeneration was the most common degenerative change accounting 79.17% cases. Similar findings were seen in the study by Geethamala et al.,[6] Kakulapati et al.[8] and Naz et al.,[9] which showed that hyaline degeneration as commonest degenerative change in 59.48, 62.5, and 88.41% of cases, respectively. Calcification was the second most common degenerative change seen in 10.41% of cases which was similar finding observed by Kakulapati et al.[8] in their study. The other degenerative changes observed in our study were one case (2.08%) each of cystic degeneration, red degeneration (apoplectic change) (Fig. 2), and myxoid degeneration. These results were similar to results in the study conducted by Gowri et al.,[10] which described hyaline change as a most common degenerative change in 16.90% followed by cystic, myxoid, calcific, and red degeneration as a least common change.

There were two cases of leiomyoma with heterologous differentiation in our study, one with osseous metaplasia and other with cartilaginous metaplasia. Review of literature showed both of this differentiation are rare to occur, and there is a single case of uterine leiomyoma with osseous metaplasia reported by Chander and Shekhar.[11–13]

Leiomyoma with apoplectic change usually seen in pregnancy or with use of oral contraceptives.[14] A single case of leiomyoma with apoplectic change was observed in our study. Patient was 26 years postpartum female presented with complaint of postpartum hemorrhage and was underwent hysterectomy. On gross examination, intramural leiomyomas measuring 6 and 4 cm, respectively, showing stellate hemorrhages were identified. Microscopically, the tumor showed patchy areas of hemorrhagic necrosis and edema surrounded by hypercellular areas with cells showing mild atypia. However, mitotic activity was sparse, and tumor cell necrosis was absent. Thus, recognition of entity is important to prevent misdiagnosis as any malignant tumor. In this case, we concluded the case as leiomyoma with apoplectic change.

The case of leiomyoma with osseous metaplasia was a 63-year-old postmenopausal female who came with complaint of pain in the abdomen and abnormal uterine bleeding. On ultrasonography, there was a mixed echogenic lesion measuring 5 × 5 × 4 cm in the uterus with foci of dense calcification. A probable diagnosis of degenerated submucous leiomyoma of the uterus was made. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The removed uterus showed a submucosal leiomyoma measuring 5 × 5 × 4 cm, which was stony hard in consistency, difficult to cut, and was kept for decalcification. The cut-section of the mass showed central bone formation (Fig. 3). The H- and E-stained sections from the decalcified bits showed foci of ossification with the formation of mature bony lamellae and peripheral hyaline degeneration surrounded by fascicles of spindle cells with indistinct cell boundaries and cigar shaped nuclei with blunt ends (Fig. 4). However, significant pleomorphism, nuclear



Figs 3A to C: (A and B) Cut surface and gross image of submucosal leiomyoma showing central bone formation in a case of leiomyoma with osseous metaplasia; (C) Cut-section of uterus with widened uterine cavity

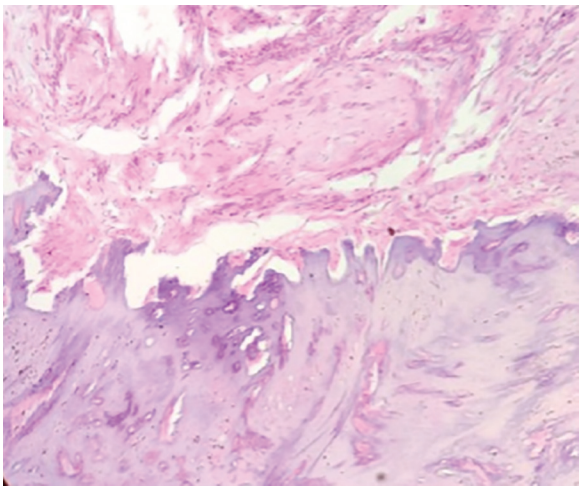


Fig. 4: Photomicrograph of leiomyoma showing osseous metaplasia with formation of mature bony lamellae and hyaline degeneration (40×)

atypia, necrosis, and mitosis were absent. Thus, a histopathological diagnosis of uterine leiomyoma with osseous metaplasia was made.

Another case was a case of 68-year-old female patient with complaint of menorrhagia and abdominal pain with clinical diagnosis of leiomyosarcoma. On gross examination, hysterectomy specimen revealed large intramural leiomyoma showing multiple, variable sized greyish white nodules, and foci of hemorrhages (Fig. 5). On microscopy, leiomyoma showed abundant mature hyaline cartilage and areas of hemorrhage surrounded by fascicles and bundles of smooth muscle cells (Fig. 6). However, nuclear atypia, mitosis, or necrosis was not evident. Thus, the final diagnosis of leiomyoma with cartilaginous metaplasia was confirmed.

In the present study of 70 cases, classical variant of leiomyoma were seen in 66 cases (94.28%). There was one case (1.43%) each of neurilemomma-like, symplastic, cellular, and lymphocyte-rich leiomyoma. The results were in analogous with the study done by Kokila et al.,[15] which showed conventional leiomyomas (88.6%) as the most common variant while symplastic, neurilemmoma-like, and cellular leiomyoma as the least common (Fig. 7).

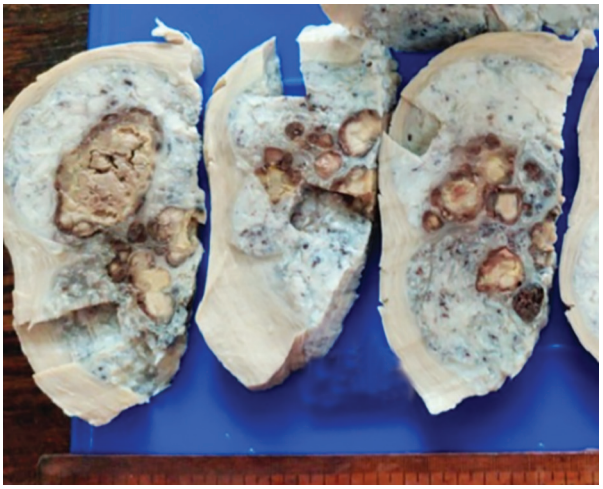


Fig. 5: Cut surface of intramural leiomyoma with multiple greyish white glistening areas with multiple necrotic and hemorrhagic foci in a case of leiomyoma with cartilaginous metaplasia

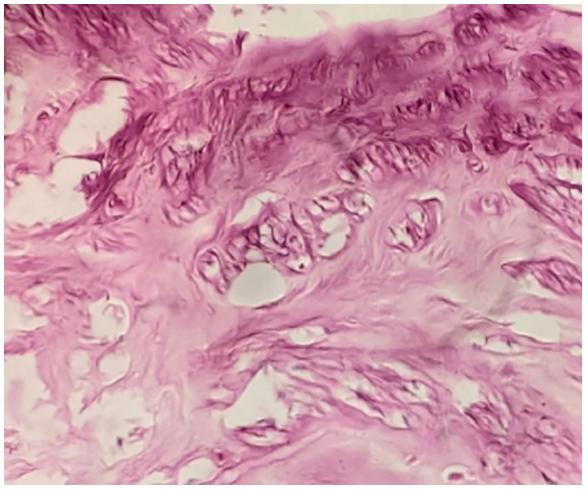


Fig. 6: Photomicrograph of leiomyoma showing cartilaginous metaplasia with inset showing mature hyaline cartilage (40×)

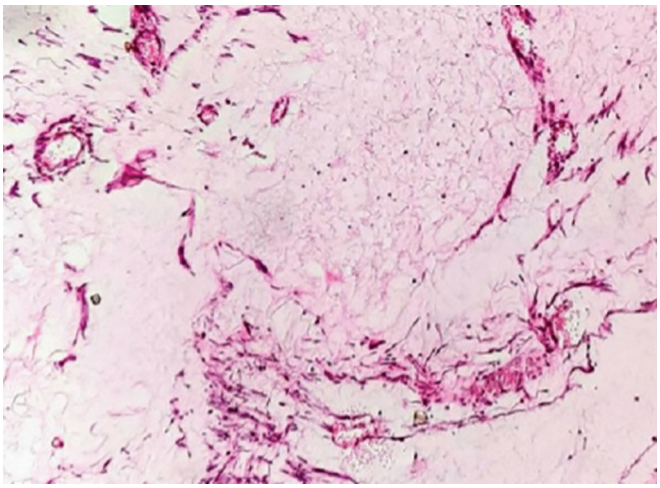


Fig. 7: Photomicrograph of leiomyoma with myxoid change (40×)

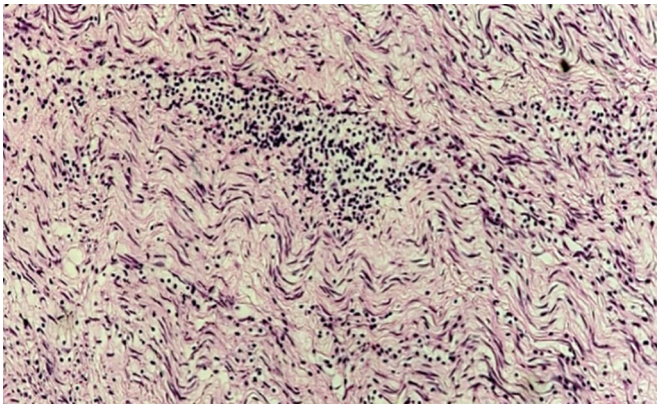


Fig. 8: Lymphocytic-rich leiomyoma (at 40× magnification)

Lymphocytic infiltration within the uterine leiomyoma is rare.[16] A case of leiomyoma with lymphoid infiltration was seen in our study, which was diagnosed in 45 years patients who presented with menorrhagia. Microscopically, the tumor was composed of scattered to diffuse infiltrate of small lymphocytes admixed with plasma cells within smooth muscle cells (Fig. 8). The main differential diagnosis were malignant lymphoma and inflammatory pseudotumor. Leiomyoma with lymphoid infiltration, on gross examination, resembles typical leiomyomas, whereas malignant lymphomas, in contrast, have softer, fleshy, poorly circumscribed appearance.

The lymphocytes in leiomyomas with lymphoid infiltration tend to be small and admixed with plasma cells and eosinophils, with the lymphoid infiltrate almost clearly confined to the leiomyomas.

In the present study, a single case of neurilemmoma-type leiomyoma was diagnosed in 50-year-old female who presented with abdominal pain. On microscopic examination, typical fascicular pattern of a leiomyoma was seen (Fig. 9). The tumor also showed focal areas showing nuclear palisading mimicking a schwannoma.[17]

Symplastic leiomyoma (atypical, bizarre, pleomorphic leiomyoma) is another mimicker of leiomyosarcoma, and it often creates a diagnostic challenge. Microscopically, symplastic leiomyoma shows moderate to severe cytological atypia with characteristic bizarrely shaped multinucleated or multilobated giant cells and hyperchromatic nuclei with abundant eosinophilic

cytoplasm (Fig. 10). Typically, uninvolved areas show the bizarre cells show bland cytologic features. Important clues in differentiating symplastic leiomyoma from a leiomyomasarcoma are the patchy or multifocal distribution of bizarre cells in the tumor, low mitotic activity (<10/10 hpf), and absence of tumor cell necrosis. One case of symplastic leiomyoma was included in our study which on microscopic examination revealed a cellular tumor showing many atypical cells with bizarre shaped nuclei showing nuclear hyperchromatism and abundant eosinophilic cytoplasm and multinucleated giant cells. These were intermingled with cells resembling usual smooth muscle. Absence of mitoses and necrosis helped to differentiate from leiomyosarcoma, and the diagnosis of symplastic or leiomyoma with bizarre nuclei was confirmed.

World Health Organization (WHO) defines cellular leiomyomas as the leiomyomas having significantly high cellularity compared to surrounding myometrium. However, there is no tumor necrosis, atypia, and mitotic figures. Their incidence is usually <5%.[6] In our study, we encountered a single case of cellular leiomyoma.

Although leiomyoma is one of the commonest uterine tumors prevalent among reproductive aged women, certain types like parasitic fibroid are rare, and among these, the primary variety is rarer.[18] Present study incorporate a case of parasitic leiomyoma in 36-year-old female patient presented with complaint of abdominal pain. On ultrasonography, there was a large uterine intramural leiomyoma and a mass in right hypochondriac region which was not attached to any pelvic organs. Clinical and radiological diagnosis of desmoid tumor or GIST was given. Biopsy of abdominal lump was performed and sent for histomorphological examination, which revealed bundles of smooth muscle cells admixed with collagenous stroma. Two differential diagnoses were given one as leiomyoma and other was desmoid tumor. Later on, the resected abdominal lump and the hysterectomy specimen were received, which showed similar histomorphological features with large areas of red degeneration within the abdominal lump and the final diagnosis of parasitic leiomyoma with large intramural leiomyoma was given. Further, the immunohistochemistry was performed which highlighted the immunostain smooth muscle actin (SMA) and vimentin. We followed up the case postoperatively, and patient is doing well after 2 years of surgery.

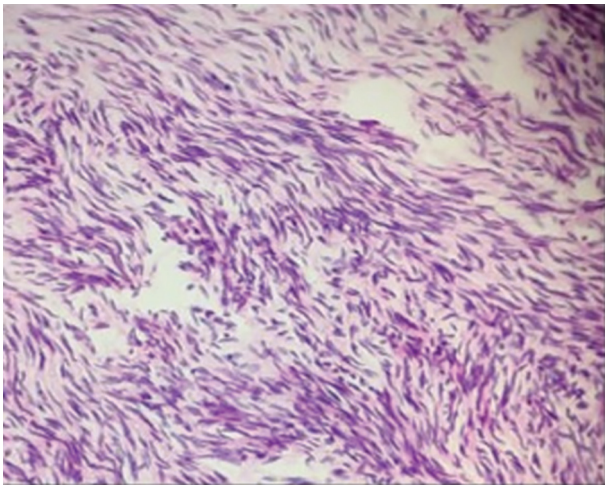


Fig. 9: Leiomyomas with schwannoma-like or neurilemmoma-like differentiation (40×)

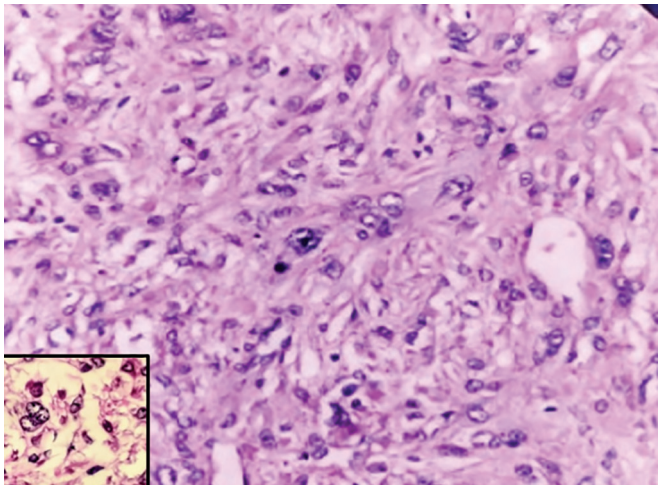


Fig. 10: Photomicrograph of symplastic leiomyoma showing irregularly shaped bizarre cells with large nuclei and inset showing a multinucleated giant cell (H&E, ×400)

Conclusion

Among all the uterine mesenchymal tumors, smooth muscle neoplasms are most common and show a wide morphologic spectrum, especially within the category of leiomyomas which is responsible for diagnostic problems. The difficulty in diagnosis is more frequent with leiomyosarcoma (including mitotically active, apoplectic, and leiomyoma with bizarre nuclei) but also with endometrial stromal tumors. There is also a diagnostic challenge in cases of leiomyomas with rare secondary changes like osseous and chondroid metaplasia. Thorough knowledge about variants of leiomyomas and secondary degenerative changes seen in leiomyoma helps us to prevent any misdiagnosis.

Vigilant histopathological examination should be done in each and every case to differentiate them from other uterine malignant tumors and to avoid unnecessary aggressive treatment and patient's anxiety.

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