Section: Pathology

Original Research Article

THE MYSTERIOUS PRESENTATION OF UTERINE LEIOMYOMA: A HISTOMORPHOLOGICAL ASSAY

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Abstract

Background: Leiomyoma is the most typical condition linked to abnormal and excessive uterine bleeding in the majority of females. Hormones are crucial for the growth and development of leiomyoma because they influence how it develops. Many a times leiomyoma presents variably revealing its many variations and subsequent alterations (secondary changes) which mimics cancer during clinical examination, radiological and grossly. Therefore, accurate understanding of alterations in leiomyoma and its variants is essential to prevent misdiagnosis. Analysis of histopathological features of variants and degenerative changes in leiomyoma which mimics malignant lesions and poses great difficulty in diagnosis, management and prognostication. **Materials and Methods:** This was a retrospective cross sectional study conducted in the department of pathology at Patna medical college and hospital (PMCH) over a period of 2 years from June 2015 to June 2017.Gross and microscopic detailed examination of leiomyoma was done for hysterectomy specimen. **Result:** A total of 3140 hysterectomy specimen with leiomyoma were analyzed, out of which 575 cases were included in the study comprising of variants and secondary changes. Usual leiomyoma were excluded from the study. Age of the patients ranged from 20 to 75years with a peak incidence seen in the 4th decade of life. Degenerative changes like hyalinization was seen maximum in 87% cases followed by hyaline and cystic change in 9% of cases, only cystic change was seen in 2% cases followed calcification, mucoidand ossification seen in 1% cases.Few of the cases showed secondary changes like cellular, symplastic/ atypical/mitotically active leiomyoma, colyledenoid, angioleiomyoma, adenomyoma and progesterone induced changes. **Conclusion:** In order to provide surgeons with an appropriate diagnosis, pathologists should be knowledgeable about all types of degenerative alterations and variants. To prevent incorrect diagnosis, it is essential to have a precise understanding of these variations and the alterations in leiomyoma.

INTRODUCTION

The benign tumors known as leiomyomas are made up of smooth muscle cells and varied levels of fibrous connective tissue. These benign uterine neoplasms, which can also go by the names fibromyomas, fibroid, or myomas affect between 5-20% of women in the reproductive age range. About 70–80% of hysterectomy specimens contain incidental or accidental findings of uterine leiomyomas. Due to unopposed oestrogen stimulation, they show a broad variety of morphological variations and subsequent alterations. Abdominal lumps, irregular uterine bleeding and abdominal discomfort are some of the signs of these tumors. Leiomyoma's histopathological characteristics vary greatly depending on the clinical presentation, location, frequency, presence of degenerative alterations and unusual variations. Although the diagnosis of a leiomyoma is simple, a small percentage of leiomyomas that present with unusual histomorphological variants and uncommon secondary changes may be mistaken for leiomyosarcomas or other endometrial lesions, creating a diagnostic challenge.

Leiomyomas appear under a microscope as whorled, anastomosing fascicles of homogeneous fusiform smooth muscle cells with blunt, elongated nuclei, thin chromatin, and fuzzy cell boundaries.[1] Common degenerative alterations include hyaline degeneration, hydropic change, mucoid degeneration, and dystrophic calcification.

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Leiomyoma subtypes that resemble malignancy in one or more ways are what make them the majority of them interesting. These subtypes include myxoid, epithelioid, cellular, haemorrhagic, leiomyoma with atypical nuclei, and leiomyoma that is mitotically active. Diffuse leiomyomatosis, dissecting leiomyomatosis, parasitic leiomyomatosis, disseminated peritoneal leiomyomatosis, intravascular leiomyomatosis, and benign metastasizing leiomyoma are some examples of smooth muscle proliferations with atypical growth patterns.

The purpose of this study was to characterize the secondary modifications and variations of leiomyomas, particularly those that resemble malignancy, and to evaluate the characteristics of these that aid in distinguishing them from malignant tumors.

MATERIALS AND METHODS

This is a retrospective cross-sectional study was conducted at the Patna Medical College Patna, in the department of pathology, over a period of 2 years, from June 2015 to June 2017. A total of 3140 hysterectomy specimens containing leiomyoma were analyzed, of which 575 cases were included in the study which includes variants and secondary changes. Ethics approval was granted by Aryabatta Knowledge University and informed consent was obtained from patients by telephone where possible. Inclusion criteria included all leiomyomas with changes. Conventional leiomyoma was excluded from the study.

The surgical specimen was fixed in 10% neutral buffered formalin for 24–48 hours. Specimens were subjected to a detailed gross examination in which well-defined, gray to yellowish spherical lesions with a rounded appearance were observed as fibroids, and details regarding their location, number, and secondary changes were noted. Multiple sections were taken from representative sites, processed, and paraffin blocks prepared for hematoxylin and eosin-stained slides (H and E). A detailed microscopic histopathological examination was performed. Histopathological changes in leiomyoma were examined for secondary changes, variants, cellularity, nuclear atypia, mitosis, and coagulation necrosis. IHC was done in hypercellular leiomyoma with which was mitotically active.

RESULTS

During the study period of two years 3140 specimens of hysterectomy was received which had leiomyoma but out of these 575 (18.31%) cases were included in study which showed leiomyoma variants and secondary changes. Maximum number of patient presenting with changes in leiomyoma were seen in the age group 41-50 years accounting to 41% followed by 31-40 years accounting to 39% as shown in [Figure 1].

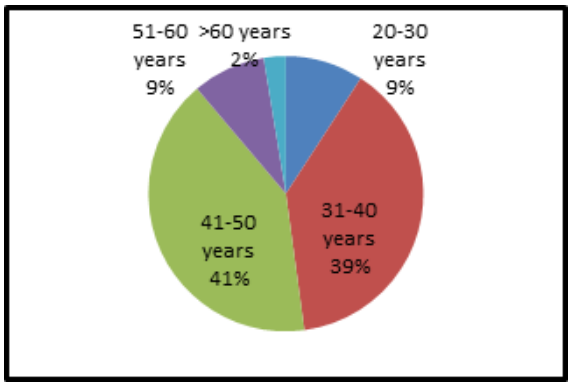

Figure 1: Age group wise distribution of cases.

Most common presentation of the female was excessive bleeding during menstrual cycle (45%) followed by pain abdomen (20%), mass abdomen (15%) and others.

Maximum number of cases showed hyaline degeneration (83%) in leiomyoma followed by hyaline and cystic (9%) degeneration as shown in figure 2 1a nd b. Only cystic degeneration was seen in 2% cases. Little rare degeneration like myxoid as shown in [Figure 2 2a and 2b] was seen in only 4 cases. And calcification was seen in 5 cases as shown in [Figure 2, 3a &3b]. The distribution of case showing secondary changes is shown in table 1.

Table 1: Distribution of cases showing secondary changes in leiomyoma.

Secondary change	Cases (N=553)
Hyaline	478
Hyaline and cystic	51
Cystic	11
Calcification	5
Mucoid	4
Ossification	2
Red degeneration	2

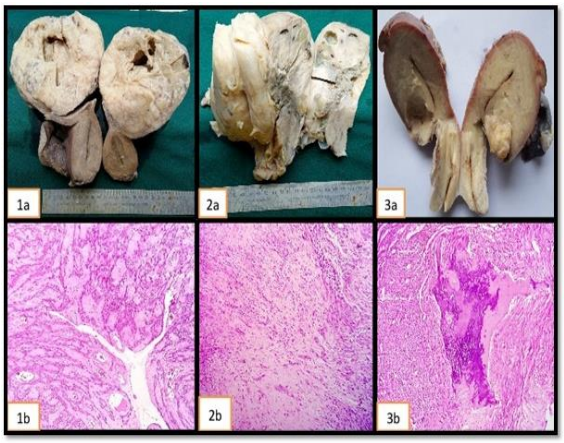

Figure 2: Gross and microscopic presentation of changes in leiomyoma - 1a &1b) hyaline and cystic degeneration 2a&2b) Myxoid degeneration 3a&3b) Calcification and ossification

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Fourteen cases of variants of leiomyomas were encountered constituting 2.5% of the cases as shown in [Table 2].

Table 2: Distribution of variants of leiomyoma.

Variants of Leiomyoma	n=14
Cellular leiomyoma	5
Symplastic/mitotically active/bizzare	3
Angioleiomyoma	2
Lipoleiomyoma	2
Cotyledenoid	1
Progesteroninduced changes	1

Variants of leiomyoma included 5 cases of cellular leiomyomas as shown in [Figure 3 1a &1b], 3 cases of bizarre (symplastic) leiomyomas as shown in [Figure 3 2a&2b], 2 cases of angioleiomyoma as shown in [Figure 4 4a and 4b], 1 case of progesterone induced change in leiomyoma shown in [Figure 4 5a and 5b], 1 case of cotyledenoid leiomyoma shown in [Figure 3 3a and 3b] and 2 cases oflipoleiomyomas assessed as shown in [Figure 4 6a and 6b]. These secondary changes and variants were found in the leiomyomas irrespective of their location

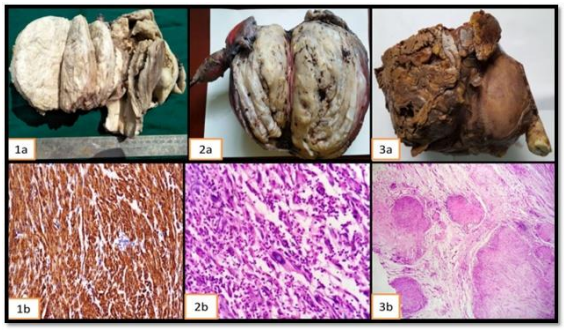

Figure 3: Gross and Microscopy of variants of leiomyoma: 1a (Cellular leiomyoma): Gross examination showing large solid serosal fibroid 1b: Microscopic examination shows cellular tumor with benign spindle cells positive for SMA in cellular leiomyoma (IHC 20x) 2a: (bizarre (symplastic) leiomyomas):Gross examination showing large subserosal mass with cystic and myxoid degeneration 2b: Microscopic examination showing scattered mitosis with atypical bizarre cells (H&E40x)3a:(cotyledenoid leiomyoma) Gross examination showing large exophytic mass protruding from post. 3b Microscopic examination showing numerous nodules containing swirls of benign spindle cells with hyaline degeneration surrounded by stromal odema (H&E 20x) in coteylednoid leiomyoma

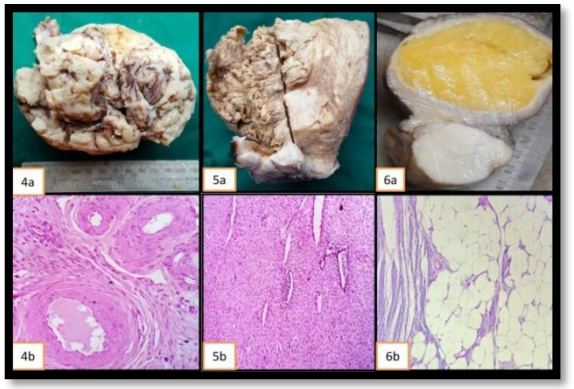

Figure 4: 4a: (angioleiomyoma) Gross examination revealed a large subserosal fibroid. 4b Interlacing fascicles of spindle cells swirling around thick walled blood vessels (H&E 40x) in angioleiomyoma5a: (progesterone induced changes in leiomyoma) Gross examination showing leafy appearance of leiomyoma 5b:Microscopic examination showing progesterone induced deciduous appearance of leiomyoma with infiltration by lymphocytes (H&E 20x) in progesterone induced changes in leiomyoma 6a: lipoleiomyoma. Gross examination of uterus showing yellowish area with surrounding grayish white areas. 6b: Microscopic examination showing adipose tissue along with surrounding interlacingin lipoleiomyoma.

DISCUSSION

The leiomyoma are the most common benign tumors of the uterus in the reproductive and post menopausal age group. The impact of environmental estrogens has only lately been investigated; howeverestrogen and progesterone are known to stimulate the formation of tumors. Growth factors with mitogenic activity, including transforming growth factor-3, basic fibroblast growth factor, epidermal growth factor, and insulin-like growth factor-I, are shown to be enhanced in leiomyoma and may be the effectors of estrogen and progesterone promotion.[1] Leiomyoma 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 leiomyoma.[2]

This study was conducted during the period of 2 years, 3140 hysterectomy specimens containing leiomyomas were analyzed, of which 575 cases (18.31%) were included in the study which includes secondary changes as shown in figure 2 and variants as shown in [Figure 3 &4].Age of patient presenting with changes in leiomyoma was seen in the age group 41-50 years accounting to 41% followed by 31-40 years accounting to 39%. This age of presentation was similar to the study by Rajendran AB. et al where 56.54% cases presented with fibroid in the age group of 41-50 years.[3] Baird DD et al., in

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their study of randomly selected women between 31-49 years found that the incidence of uterine fibroids was 60% by age 35 years which increased to 80% by age 50 years in African-American women and for Caucasian women by 35 years of age the incidence of uterine fibroids was 40% and by age 50 years it was found to be 70%.[4] Lahori M et al in his study was similar to our study that highest numbers of patients included in this study were between 41-50 years (46.82%).[5]

Several secondary changes and histological variants of uterine smooth muscle tumours have been identified. Secondary changes occurring in leiomyomas are detectable in approximately 56% of cases is similar to study by janu A et al where secondary changes in leiomyoma was seen in 65% cases.The secondary changes in leiomyoma that were seen in our study were hyaline, hyaline and cystic, cystic, calcification, mucoid, ossification and red degeneration was almost similar to study by janu Abraham et al which include hyaline change, mucoid, myxoid or myxomatous change, calcification, cystic changes and fatty metamorphosis.[1]

In our study 83% cases showed hyaline degeneration which was the maximum followed by hyaline and cystic (9%) cases and only cystic degeneration was seen in 2% cases. Goyal V et al,[6] in his study stated that secondary degenerative changes were observed in 44 cases (29.3%), hyaline degeneration was the most common secondary change and found in 25(56.8%) followed by myxoid degeneration seen in 6 cases (13.6%) myxoid degeneration Pre-op mimics ovarian tumor and intra-op LMS. Histopathology remains the gold standard. Accumulation of acellular material rich in acid mucin. Myxoid stroma arises from myxoid degeneration of collagen surrounding smooth muscle nodule and leaving large vessels behind is not seen in LMS. Nggada et al,[7] also observed secondary changes in 21% cases of all leiomyoma and most common change was hyalaine degeneration. In adequate blood supply is the root cause of degenerative changes in leiomyomas, which are typically seen in big, long-standing leiomyomas, particularly intramural leiomyomas.

Histological variants seen in our study are cellular leiomyomas seen in 5 cases in our study. The WHO defines as leiomyomas with cellularity that is considerably higher than that of the surrounding myometrium.Scant cytoplasm with increased mitotic activity, and scattered bizarre cells and atypia is seen. the gross shows irregular borders.[1]A differential of Cellular leiomyoma and endometrial stromal tumors (EST) was considered with the need for immunohistochemistry (IHC) testing for confirmation. IHC testing with CD10, smooth muscle actin (SMA), and caldesmon revealed that the tumor cells were positive for SMA as shown in [Figure 3 1b] and caldesmol, whereas negative for CD 10, thereby confirming the diagnosis of cellular leiomyoma.[8] Highly cellular leiomyoma is now considered as distinct entity. The cellularity of highly cellular leiomyomas is comparable to that of ordinary endometrial stromal tumours. These are frequently mistaken for either low grade endometrial stromal sarcomas or stromal nodules.[1]

Symplastic/ mitotically active / bizarre leiomyoma were seen in 3 cases in our study which generally mimics leiomyosarcoma (LMS) and smooth muscle tumor of uncertain malignant potential (STUMP). Table 3 however differentiates between the mitotically active leiomyoma with leiomyosarcoma and smooth muscle tumors of uncertain malignant potential (STUMP).

Table 3: Difference between leiomyosarcoma (LMS), Smooth muscle tumor of uncertain malignant potential (STUMP) and Mitotically active leiomyoma on the basis of tumor necrosis, atypia and mitosis.

Tumor necrosis	Atypia	Mitosis/10HPF	Diagnosis
Absent (-)	Present(+)	≥10	Leiomyosarcoma (LMS)
Present (+)	Present (+)	≥10	
Present (+)	Present (+)	<10	
Absent (-)	Absent (-)	>15	Smooth muscle tumor of uncertain malignant potential(STUMP)
Absent (-)	Present (+)	<10	
Present (+)	Absent (-)	<10	
Absent (-)	Absent (-)	≥6 and ≤15	Mitotically active leiomyoma

Symplastic/ mitotically active / bizarre leiomyoma shows presence of strangely shaped multinucleated and multilobated large cells with hyper chromatic nuclei and a lot of eosinophilic cytoplasm, as well as noticeable nuclear pseudo inclusions and scattered atypical nuclei, is what distinguishes this tumour under the microscope. Usually, the regions where the strange cells are not present have unremarkable cytological characteristics. The distribution of bizarre cells in the tumor, which is patchy or multifocal, is the key indicator for distinguishing bizarre leiomyoma from a malignant tumor. Low mitotic activity and a lack of necrosis in cancer cells are further beneficial characteristics. Pre-op diagnosis can be made by MRI, FDG-PET, transcervical needle biopsy and IHC. In our case IHC SMA was performed as shown in [Figure 2 1b].LMP2 and Ki67 is low in symplastic as compared to LMS.Pre-op accurate diagnosis will help in uterus preserving options like GNRH analogues, uterine artery embolisation.

Cotyledenoid leiomyoma/Sternberg tumor is one of the rare entity and is seen in one of our cases. Only 30 cases have been documented in the literature. It is more prevalent in the fourth to fifth decade marked by intramural dissection and an extrauterine

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component that resembles the placenta, alarming gross sight that looks like malignancy yet is entirely benign.

Angioleiomyoma (AL) is seen two of the cases presenting a s subserosal mass. Subserosal large masses are difficult to differentiate from primary ovarian neoplasm pre-op specially with raised CA125 levels. Histopathology is the gold standard. Blood vessels in conventional leiomyomas are capillaries, arterioles or small arteries in contrast to thick walled vessels in AL. Atypical mitosis, coagulative necrosis & hypercellularity mimics LMS. Important to recognize as highly vascular and may undergo spontaneous rupture.

Progesterone induced changes include infarct type necrosis, increased cellularity, mitosis, nuclear pyknosis, epithelioid morphology, stromal edema, myxoid change & infiltration by lymphocytes is seen in progesterone induced changes in leiomyoma which is seen in one cases in our study. It generally mimics leiomyosarcoma and Smooth muscle tumor of uncertain malignant potential (STUMP).

A rare variation of the very frequent uterine leiomyoma is a uterine lipoleiomyoma.[9]Lipoleiomyomas are uncommon, benign tumours made up of mature adipocytes and smooth muscle cells combined together. According to reports, uterine lipoleiomyomas account for 0.03% to 0.2% of all uterine leiomyomas.[9] In our study two cases of lipoleiomyoma is encountered.

CONCLUSION

The increased incidence of uterine leiomyomas and the absence of overt signs and symptoms in most cases are important issues for early detection of the disease. Pain is most common symptom of degenerative change and is commonly seen during 45-50years of age. Pre-op large leiomyomas are difficult to differentiate from malignancies on imaging alone so histopathology remains the gold standard. Pathologists should be aware of all sorts of degenerative changes and variants to guide the surgeons with accurate diagnosis. They should always be alert with the overlapping findings of benign and malignant lesions.

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