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HISTOMORPHOLOGICAL SPECTRUM OF UTERINE LEIOMYOMA VARIANTS – A RETROSPECTIVE STUDY IN TERTIARY CARE HOSPITAL

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ABSTRACT

To study the histomorphological spectrum of uterine leiomyoma variants. This study is done over a period of three year (May 2019 to May 2022) in the Department of Pathology, LNMC, Bhopal. Total of 316 hysterectomy and 14 myomectomy specimens were studied. Specimens were fixed in formalin and paraffin embedded. H&E stained tissue sections were studied. In the study we performed retrospective analysis of hysterectomy and myomectomy specimen and 330 cases of leiomyoma were evaluated. Among 330 cases, 316(95.75%) were hysterectomy specimen for varying indication and 14(4.24%) were myomectomy specimen. Histologically the usual leiomyomas was comprising of 164(49.69%) cases followed by hyalinised leiomyoma 70(21.21%), myxoid leiomyoma 15(4.54%), hydropic change 12(3.63%), cellular 11(3.33%), lipoleiomyoma 10(3.03%), calcification 10(3.03%), infarct type necrosis 10(3.03%), mitotically active 8(2.42%), symplastic 7 (2.12%), schwanonian 6(1.81%), epithelioid 3(0.90%), dissecting leiomyoma 2 (0.60%) and stromal metaplasia (osseous and cartilaginous) 2(0.60%). Leiomyoma is the commonest benign smooth muscle tumor of the uterus with a number of histological variants. In this study conventional leiomyoma being the commonest variant followed by hyalinized leiomyoma, myxoid leiomyoma, hydropic leiomyoma and lipoleiomyoma. It is important to categorise various types of leiomyoma on histology to avoid misdiagnosis.

KEYWORDS: Histopathology, Fibroids, Leiomyoma variants, Hysterectomy, Myomectomy, Immunohistochemistry (IHC)

INTRODUCTION

Uterus is the crucial reproductive organ of female which is responsive to hormones. Various benign and malignant tumors arise within the uterus (1). Unopposed estrogenic stimulation manifests as leiomyomas undergoing secondary changes, endometrial proliferation or hyperplasia and other associated pathological findings (2). Uterine leiomyomas are the benign monoclonal smooth muscle tumors which arise from the underlying myometrial tissue within the uterus and are the only most typical indication for hysterectomy.(3-4).

Leiomyoma arises in any part of the uterus under the influence of local growth factors and sex hormones like estrogen and progesterone (5). Less common locations of leiomyoma are vulva, vagina, cervix, broad ligament and ovary. Leiomyoma is commonly associated with heavy or abnormal uterine bleeding, pelvic pain or pressure, infertility and recurrent pregnancy loss (6). Menorrhagia is the most frequent clinical presentation seen with intramural leiomyoma since it interferes with the myometrium contraction, whereas metrorrhagia is usually related to submucosal leiomyoma due to the endometrial ulceration (7). The gold standard for the treatment of uterine leiomyomas has traditionally been surgery, which typically consists of either a hysterectomy or a myomectomy (5).

Most common leiomyomas are conventional type. Some important examples of the subtypes of leiomyoma being atypical, cellular and mitotically active leiomyoma, hydropic ,myxoid change, hyaline degeneration, fatty degeneration, Calcific degeneration, Neurilemmoma like, lipoleiomyoma, angioleiomyoma, dissecting leiomyoma.(8) On gross examination, uterine leiomyomas are circumscribed with a solid rubbery firm texture and bulging cut surface. They are generally white but if degeneration is present, the color (red, brown or yellow) and texture (edematous, fleshy or necrotic) could also be different. Histologically, leiomyomas are composed of elongated smooth muscles with eosinophilic cytoplasm and a centrally located cigar shaped nucleus. Leiomyoma variants have similar symptoms and findings in the pelvic examinations of patients with ordinary leiomyoma and

Leiomyosarcoma. Immunohistochemistry, molecular-genetic analysis, and imaging techniques have a limited benefit for the differential diagnosis of these uterine mesenchymal tumors (9).

OBJECTIVE

Purpose of this study was to evaluate the varied histomorphological features of uterine leiomyoma variants from hysterectomy and myomectomy specimen received from Obstetrics & gynaecology department.

MATERIAL AND METHODS

In this study, we performed the retrospective analysis of hysterectomy and myomectomy specimens from May 2019 to May 2022 in L.N. Medical College & J.K. Hospital, Department Of Pathology, Bhopal. Details regarding age, clinical presentation were collected from the medical records.

A total of 330 specimen of hysterectomy and myomectomy specimen were included in this study.Inclusion criteria was all biopsies of uterine leiomyomas of any age. Exclusion criteria was insufficient or autolysed biopsy specimen.Detailed macroscopic findings including the location in the uterus (intramural, submucosal and subserosal), single or multiple, size, appearance, circumscription and cut surface (color, hemorrhage, infarction, calcification and consistency) were noted. Anatomical location of leiomyoma, number and secondary changes were examined. The specimen was then fixed overnight in 10% buffered formalin. Gross with adequate sampling was performed. Multiple parallel sections were made and their cut surface was examined. Tissue bits from representative areas were taken and processed in various concentrations of ethanol, xylol. Block were prepared for further histopathological examination. Multiple sections of five micron thickness were cut and stained routinely with Hematoxylin and Eosin. Slides were mounted with DPX and diagnosis was made according to standard guidelines. No special stain were used. All the data was analysed in SPSS version.

RESULTS

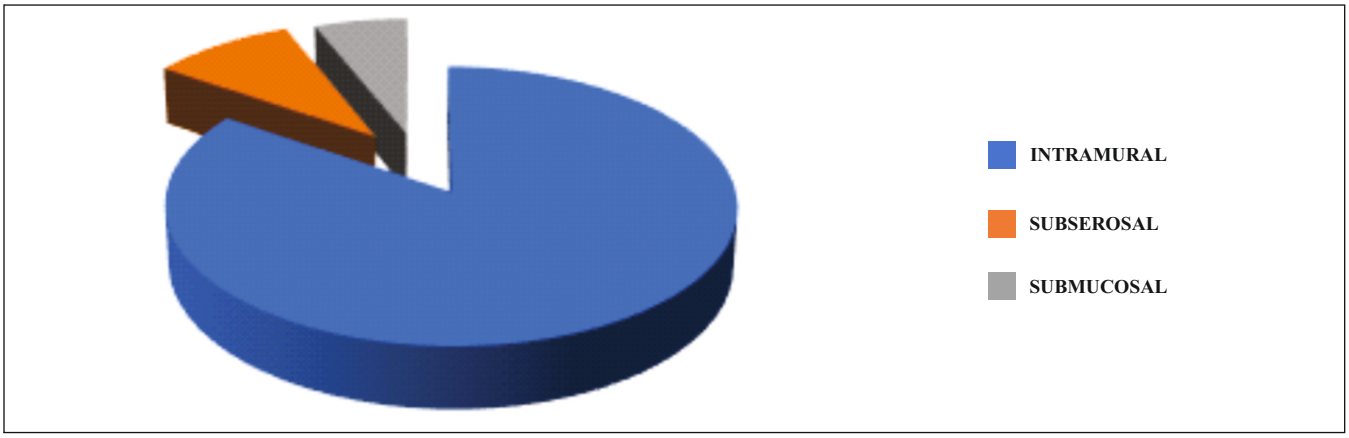
In the study we performed retrospective analysis of hysterectomy and myomectomy specimen and 330 cases of leiomyoma were evaluated. The age range was from 25-60 years. (Table 1) Among 330 cases, 316(95.75%) were hysterectomy specimen for varying indication and 14(4.24%) were myomectomy specimen. Among 330 cases maximum cases were of 279 (84.54%) intramural leiomyoma, 31 (9.39%) of subserosal leiomyoma and 20 (6.06%) of submucosal leiomyoma. (Table 2, Pie Chart 1) Most of the patients presented with clinical presentations of menorrhagia, abdominal mass and dysmenorrhoea. Other less frequent presentation were infertility and recurrent abortion. Gross features were noted. (Table 3) Histologically the usual leiomyomas was comprising of 164(49.69%) cases followed by hyalinised leiomyoma 70(21.21%), myxoid leiomyoma 15(4.54%), hydropic change 12(3.63%), cellular 11(3.33%), lipoleiomyoma 10(3.03%), calcification 10(3.03%), infarct type necrosis 10(3.03%), mitotically active 8(2.42%), symplastic 7(2.12%), schwanonian 6(1.81%), epithelioid 3(0.90%), dissecting leiomyoma 2(0.60%) and stromal metaplasia (osseous and cartilaginous) 2(0.60%). (Table 4 , Figure 1,2,3)

AGE GROUP IN YEARS	NUMBER OF CASES	PERCENTAGE
25-35	**78**	**23.63%**
36-45	**176**	**53.33%**
46-55	**67**	**20.30%**
>55	**9**	**2.72%**
TOTAL	**330**	**100%**

Table 1: Age Wise Distribution of Patient with Leiomyoma

LOCATION	SINGLE LOCATION	MULTIPLE LOCATION	TOTAL NUMBER	PERCENTAGE
Intramural	196	83	279	84.54%
Subserosal	14	17	31	9.39%
Submucosal	11	9	20	6.06%

Table 2: Location & Number of Leiomyoma in Uterus



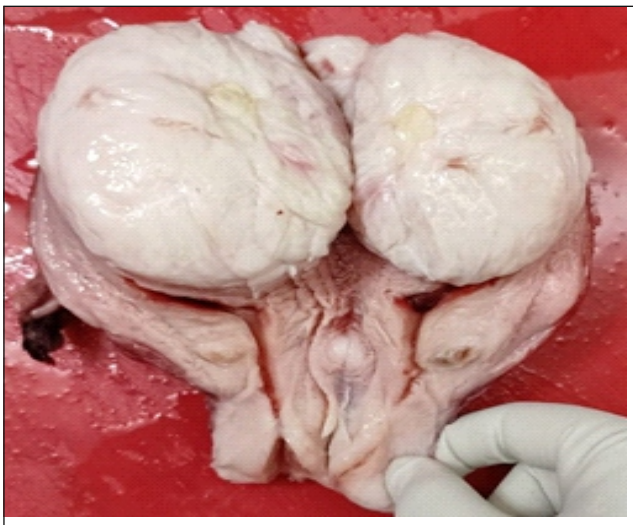
PIE CHART 1

CHIEF COMPLAINTS	NUMBER OF CASES	PERCENTAGE
Menorrhagia	**135**	**40.90%**
Mass abdomen	**41**	**12.42%**
Pain abdomen	**38**	**11.51%**
Dysmenorrhea	**32**	**9.69%**
Primary infertility	**3**	**0.90%**
Recurrent abortion	**2**	**0.60%**
Asymptomatic	**79**	**23.93%**

Table 3: Chief Complaints in Patients with Uterine Leiomyoma

TYPES	NUMBER OF CASES	PERCENTAGE
Conventional/ Usual leiomyoma	**164**	**49.69%**
Hyaline	70	21.21%
Myxoid	15	4.54%
Hydropic change	12	3.63%
Cellular	11	3.33%
Lipoleiomyoma	10	3.03%
Calcification	10	3.03%
Infarct type necrosis	10	3.03%
Mitotically active	8	2.42%
Symplastic	7	2.12%
Schwanonian	6	1.81%
Epitheiliod	3	0.90%
Dissecting leiomyoma	2	0.60%
Stromal metaplasia (osseous and cartilaginous)	2	0.60%

Table 4: Variants of Uterine Leiomyoma's Observed in Present Study



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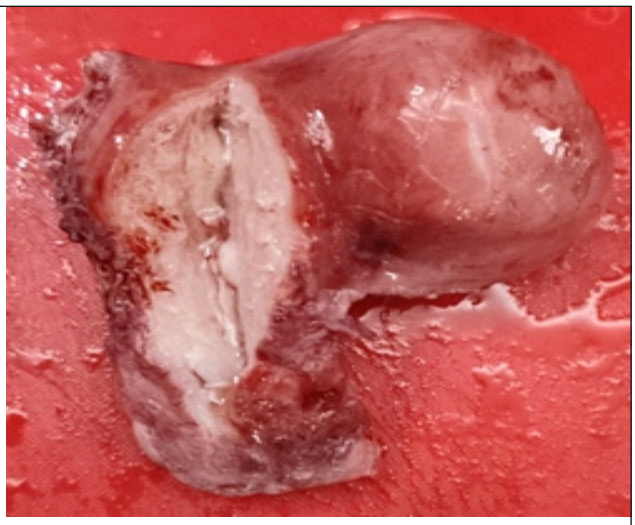

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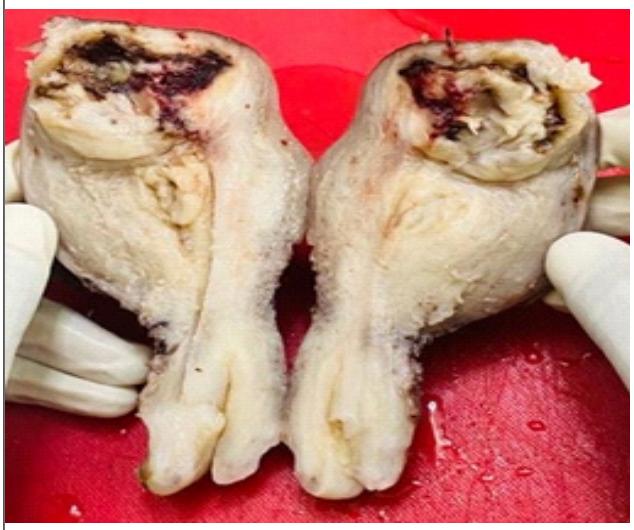

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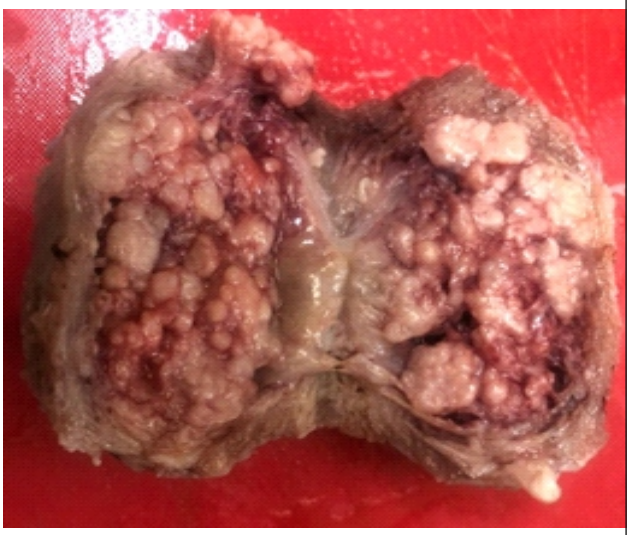

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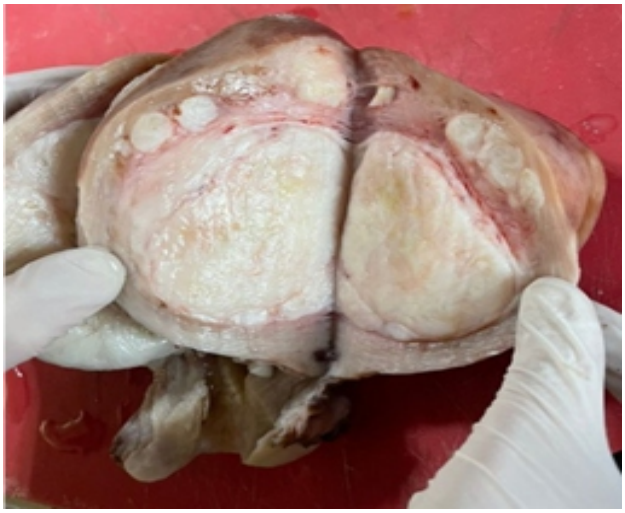

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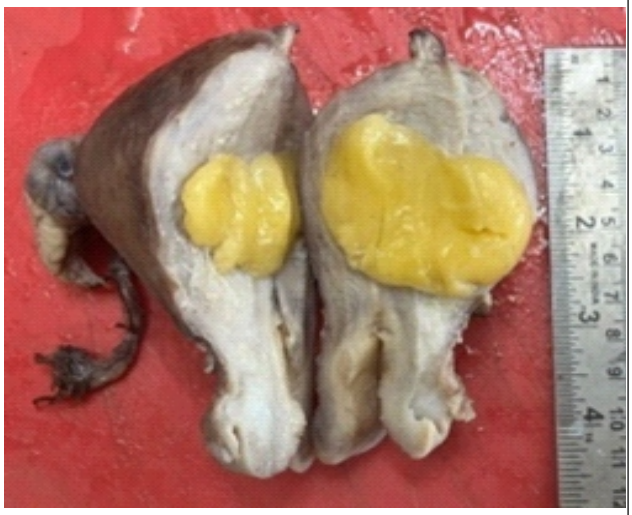

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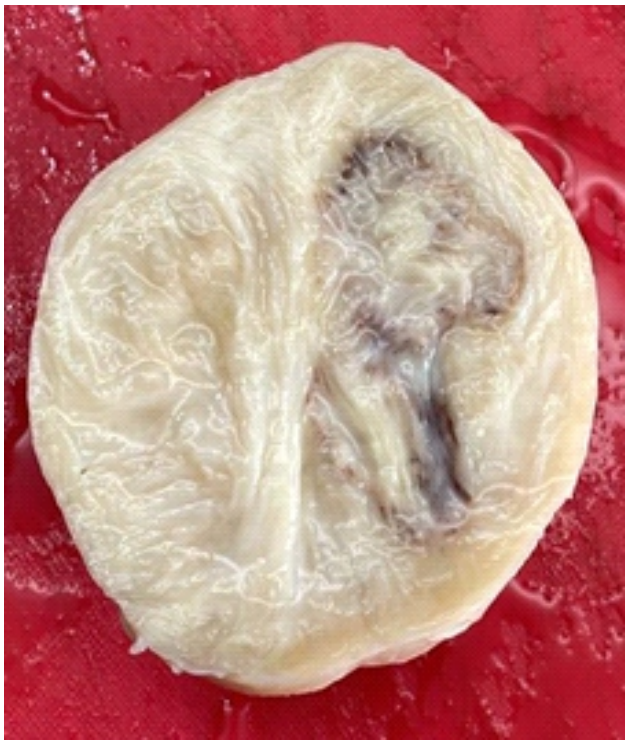
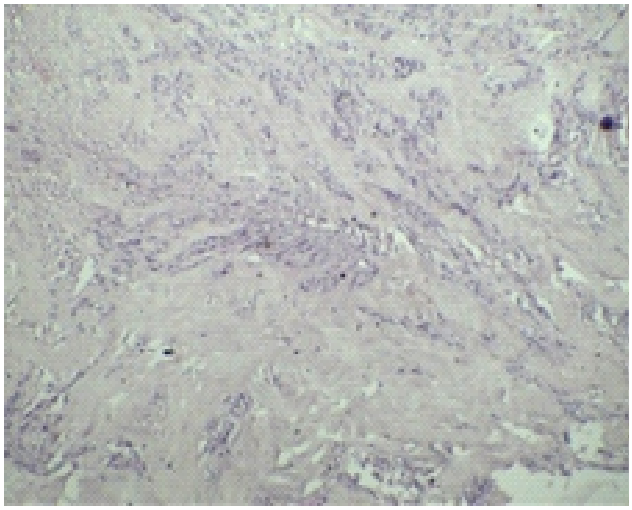


Fig 1 (h)

Figure 1: Gross Appearance of Hysterectomy / Myomectomy Specimens: (a), Well Defined Unencapsulated firm Intramural leiomyoma. Cut Surface is white, Bulging and Whorled. (b), Well Defined Subserosal Fibroid. (c), Red Degeneration - Well Defined Reddish, Hemorrhagic Leiomyoma. (d), Dissecting / Cotyledenoid Leiomyoma – Reddish Exophytic Placenta Like Appearance With Lobulated Mass and Patchy Nodules of Different Sizes. (e), Multiple Fibroids (intramural, Submucosal And Subserosal) In Uterus. (f), Lipoleiomyoma – Yellowish Mass Obliterating The Endometrial Cavity. (g), Cervical Leiomyoma – Cervix Consisting Greyish White Bulging Whorled Mass. Adjacent Dilated Endometrial Cavity Showing Endometrial Adenocarcinoma. (h), Myomectomy Specimen Showing Pale to Blackish Areas.



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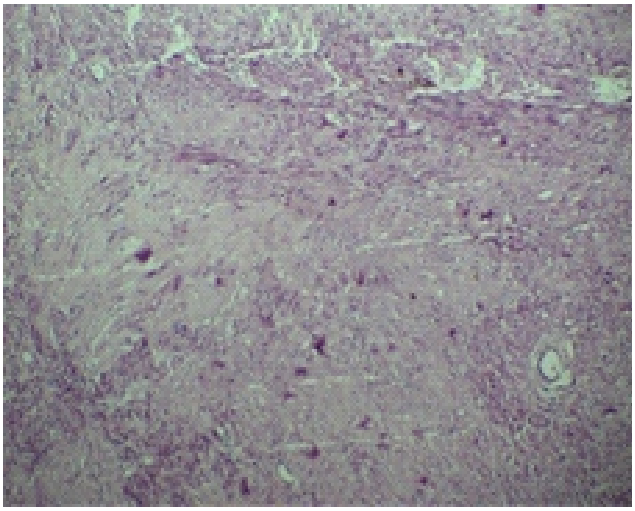

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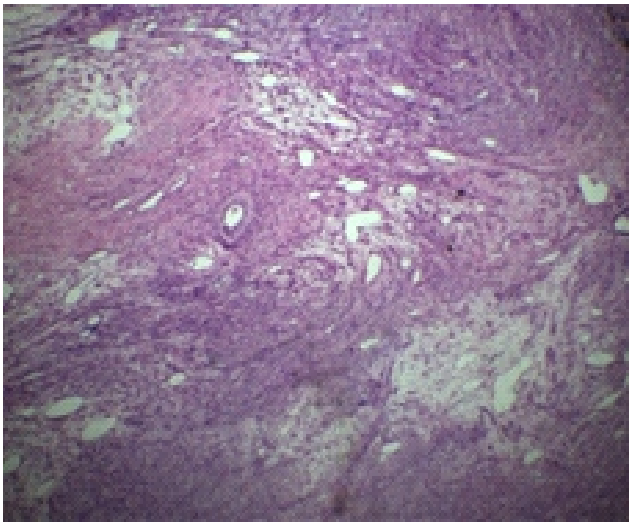
Fig 2 (c)



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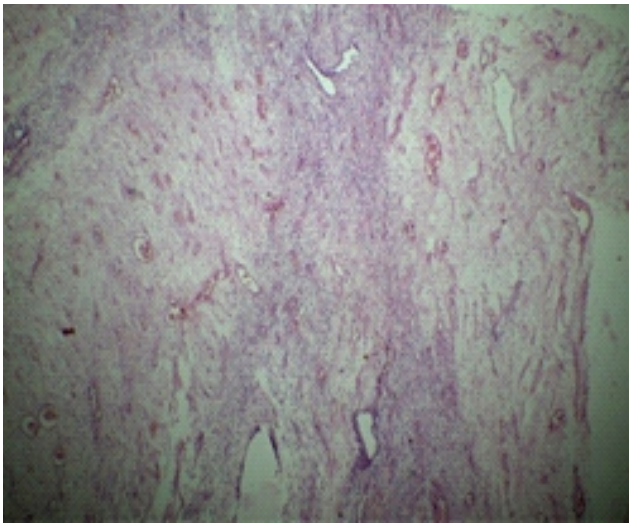

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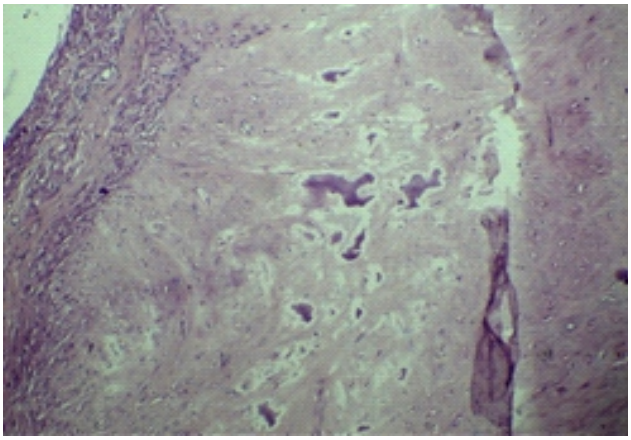


Fig 2 (f)

Figure 2: Histopathological Images Of The Variants of Leiomyomas. (a, b), Hyaline Changes – Homogeneous Eosinophilic Bands Or Plaques In Extracellular Space. (c), Infarct type Necrosis – Zone of Hemorrhage and Infarction. (d,e), Hydropic Changes – Cells Separated By Eosinophilic Proteinaceous Fluid. (f), Osseous Metaplasia – Spindle Cells Arranged in Fascicles With Bony Trabeculae and Hyalinised Areas Seen.

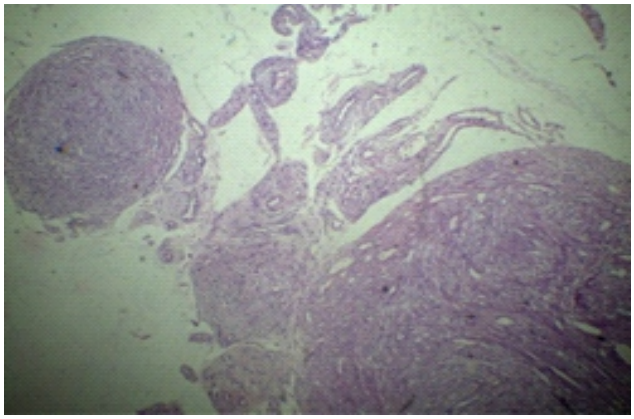
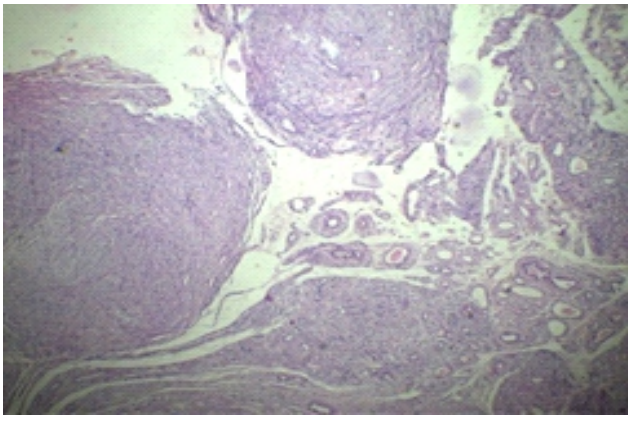


Fig 3 (a)



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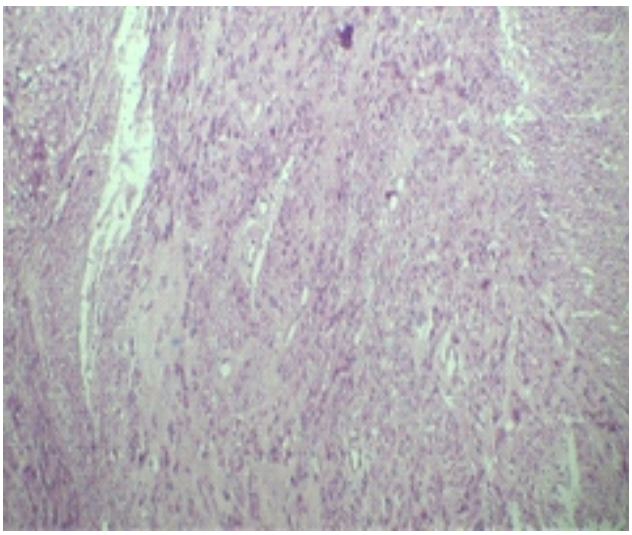

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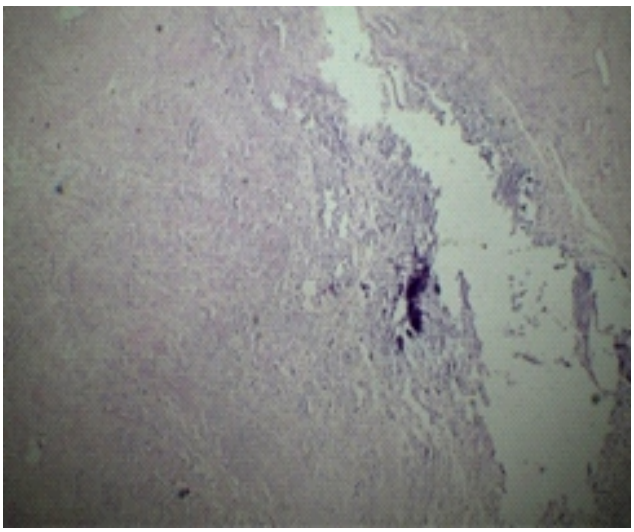

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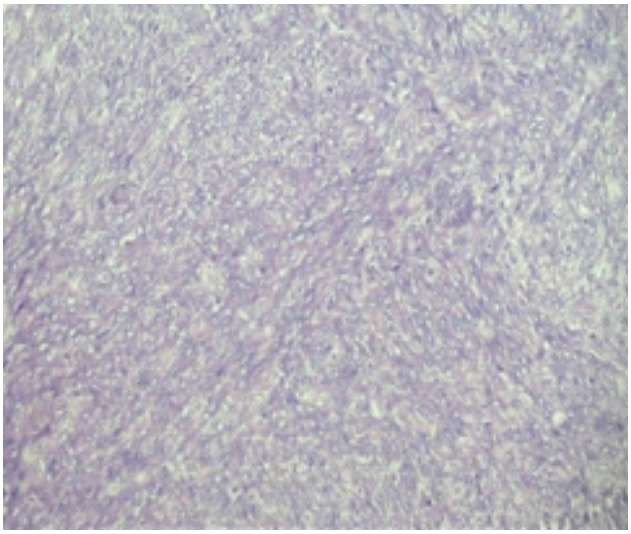

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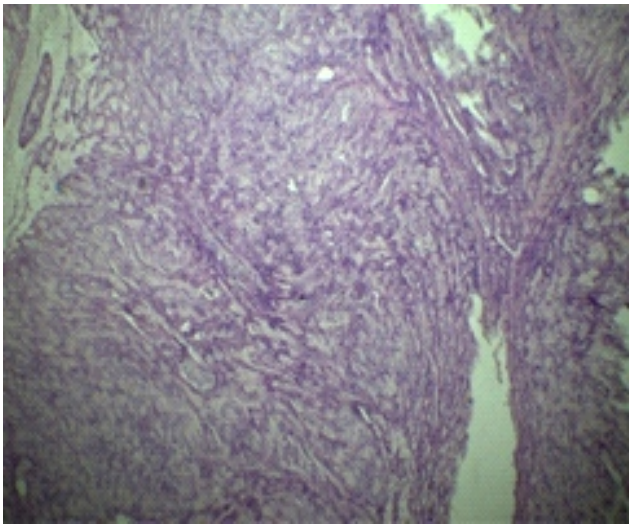
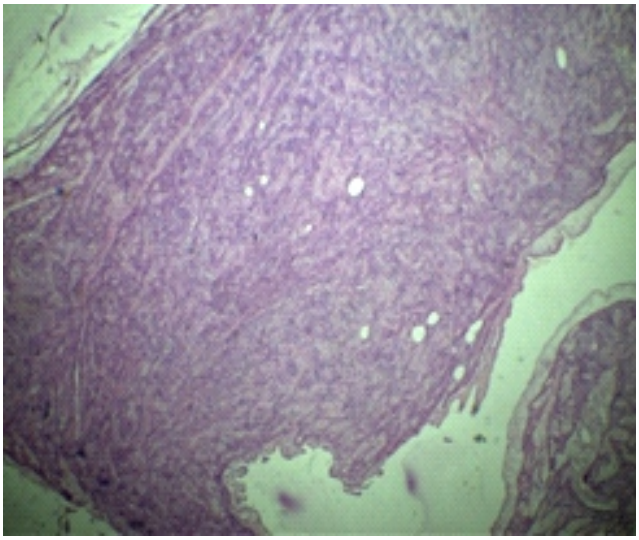


Fig 3 (g)



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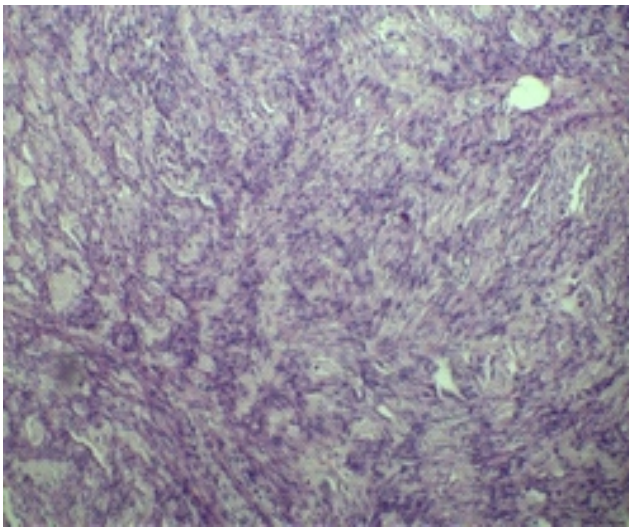

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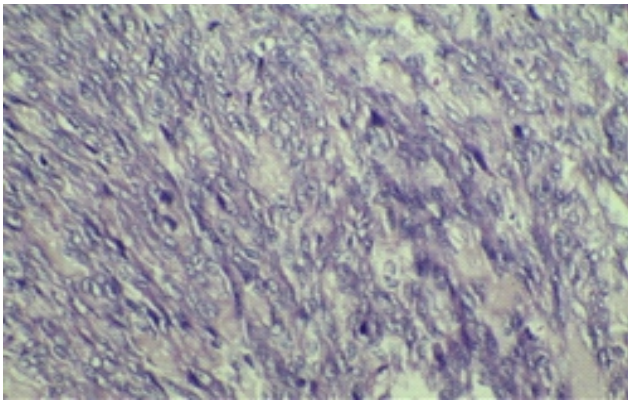

Fig 3 (i)

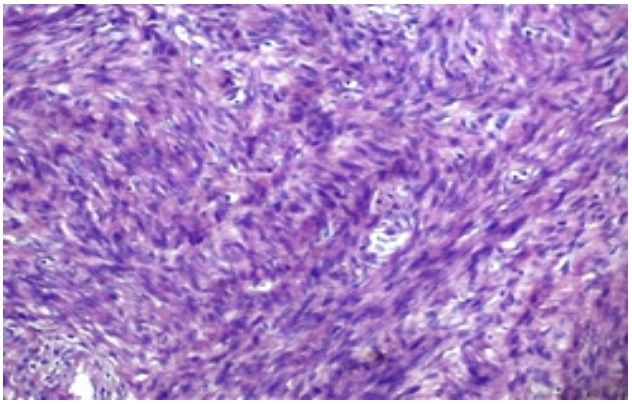

Fig 3 (j)

Figure 3: Histopathological images of the variants of leiomyomas.(a-b), Cotyledenoid leiomyoma – Nodules of smooth muscle cells dissecting the myometrium.(c), Cartilaginous metaplasia – Mature hyaline cartilage surrounded by smooth muscle bundles.(d), Epithelioid leiomyoma – Round, polygonal cells with eosinophilic cytoplasm in nested or trabecular architecture without atypia / necrosis. (e),Lipoleiomyoma – Smooth muscle cells admixed with mature adipocytes. (f),Calcification – Deep basophilic staining granular deposition over tissue section.(g-h), Schwanonian – Smooth muscle cells with hypercellular Antoni A areas and myxoid hypocellular Antoni B areas. (i),Leiomyoma with bizarre nuclei – Bizarrely shaped, hyperchromatic cells.(j), Mitotically active leiomyoma – Spindle cell leiomyoma without atypia or tumor cell necrosis with increased mitotic activity.

DISCUSSION

Leiomyoma in the uterus is a frequent condition that might have or not have aberrant findings. Leiomyomas are benign tumours of the uterine myometrium that affect women of reproductive age.

A total of 330 cases were reviewed during the three year study period. Majority of the patients , 316(95.75%) had hysterectomy while 14(4.24%) had myomectomy. 14(4.24%) that opted for myomectomy were in the age range 25 – 39 years, while 316(95.75%) that had hysterectomy were aged 35 years and above. This shows that younger women who have not completed their family opted for myomectomy and the older women opted for hysterectomy. Present study showed menorrhagia as the predominant presenting chief complaints of the patients accounted 40.90%.This finding was consistent with the studies done by Bolde SA et al..(16) Most common location of leiomyoma was intramural (84.54%) in the present study. This observation was analogous to the study done by Bolde SA et al.(16) and Baral RS et al.. (17) In this study, degenerative changes showed hyaline degeneration being the commonest accounting for 21.21% of cases. Similar findings were seen in the study by Bolde SA et al and Baral RS et al which showed that hyaline degeneration as commonest degenerative change.(16,17)

Conventional / usual leiomyoma are normocelular with well defined borders, Intersecting fascicles of monotonous spindle cells with indistinct borders, eosinophilic cytoplasm, cigar shaped nuclei (with tapered ends) and small nucleoli. Atypia is absent or mild. Mitoses is rare. In Hydropic leiomyoma the tumor cells are separated by watery or eosinophilic and proteinaceous fluid, resulting in a trabecular or nested architecture.Cotyledonoid dissecting leiomyoma is a benign smooth muscle neoplasm with an unusual growth pattern that is characterized by intramural dissection within the uterine corpus and often a placental-like appearance macroscopically in its extrauterine component.(12) On microscopy Nodules of smooth muscle cells dissecting the myometrium seen.

An extrauterine lipoleiomyoma was also described as a myolipoma, a rare benign lesion consisting of smooth muscle and regularly distributed mature adipose tissue. Macroscopically, these tumors are usually round or oval and sausage-shaped as well as multilobulated and solid in configuration . They were well-circumscribed and moderately firm with a cut surface of yellow fat localizing or diffusing into the gray smooth muscle tissue . Microscopically, the tumors were characterized by smooth muscle cells and fibrous tissue arranged in interlacing fascicles amidst mature adipocytes and surrounded by a thin myometrium layer.

Epithelioid morphology with atypical or bizarre nuclei , sometimes together with numerous lipoblasts, are the feature of bizarre or atypical lipoleiomyomas , and the absence of mitotic activity was a prominent feature to differentiate lesions from liposarcomas.(13) 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. Leiomyoma with bizarre nuclei (also called atypical, symplastic and pleomorphic) show the presence of scattered large atypical cells. These atypical smooth cells have abundant eosinophilic cytoplasm, irregular nuclear shapes and multinucleation. The nuclei are hyperchromatic often with intranuclear inclusions.(14) Symplastic leiomyoma (atypical, bizarre, pleomorphic leiomyoma) is another mimicker of leiomyosarcoma, and it often creates a diagnostic challenge. . Important clues in differentiating symplastic leiomyoma from a leiomyomasarcoma are the patchy or multifocal distribution of bizarre cells in the tumor, low mitotic activity (<10/10hpf) and absence of tumor cell necrosis.(16) Hyaline degeneration involves the presence of homogeneous eosinophilic bands or plaques in the extracellular space, which represent accumulation of proteinaceous tissue.

Myxoid degeneration involves the presence of gelatinous intratumoral foci at gross examination that contain hyaluronic acid–rich mucopolysaccharides. It is a hpocellular tumor composed of cells separated by myxoid matrix. Red degeneration is a subtype of hemorrhagic infarction of leiomyomas that often occurs during pregnancy. It is characterized by a red (hemorrhagic) appearance of the leiomyomas at gross examination (15).

Uterine smooth muscle tumors (SMTs) have been distinct in benign leiomyomas and malignant leiomyosarcomas on the basis of the cytological atypia, mitotic rate and presence or absence of the tumor cell necrosis. The Stanford criteria for the histologic diagnosis of malignant SMT (leiomyosarcoma) reported by Bell et al. included at least two of the following criteria: diffuse moderate to severe atypia, mitotic count of at least 10 mitotic figures (MF)/10 high power fields (HPFs) and tumor cell necrosis. Mitotically active leiomyoma is defined as a tumor with a high mitotic index (>5 and <19 mitoses per high-power field) and is now considered as a benign variant of leiomyoma and differs from STUMP due to the lack of recurrences and metastases outside the pelvis.(10) In Kempson's scheme, it is designated as STUMP if the mitotic activity is higher than 15. Absence of coagulative necrosis, mitotic count per 10 HPF equal or less than 10, moderate-to-severe focal atypia. This is referred to AL-LRR in Kempson's scheme.(11) Schwanonian leiomyoma shows the biphasic pattern comprising of hypercellular Antoni A and myxoid hypocellular Antoni B areas. Nuclear palisading is often seen in cellular areas. Immunohistochemical (IHC) markers positive for leiomyoma are Desmin, h-caldesmon, Smooth muscle actin, Transgelin. Smooth muscle markers can be weak in epithelioid and myxoid leiomyomas.

CONCLUSION

The present study highlights the different histomorphology of the lesion which explains the different clinical manifestations. These tumor are benign but some of the variants and secondary changes create diagnostic difficulties. However secondary changes and morphological variants of leiomyoma especially those with increased cellularity, increased mitoses and nuclear atypia create diagnostic problem. A thorough examination with adherence to standard diagnostic criteria is required to confirm the diagnosis. Therefore, a complete histopathological examination should be made mandatory for confirm diagnosis, further management and complete treatment of the concerned patients.

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