

Secondary Changes and Histologic Variants in Uterine Leiomyoma: A Comprehensive Two Year Study

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Abstract

Background: Leiomyoma which is the commonest visceral neoplasm affecting females in reproductive age group has many secondary changes as well as recognized histological variants, some of which pose diagnostic problems in differentiating from malignant neoplasms like leiomyosarcoma. Intravascular leiomyoma, a rare variant though benign in nature, has a metastatic potential because of vascular invasion.

Aim: The present study is undertaken, to study and analyze various histopathological changes within uterine leiomyomas.

Methods and material: The study included all leiomyoma cases received over a period of 2 years. After taking relevant clinical data, a proper gross examination was done before the representative areas were sectioned, processed, stained and studied in detail under a light microscope. Clinical, gross and histological features were correlated.

Results: A total of 348 specimens were received. multiparous women were the most effected with a peak incidence in the 4th decade of life. Menorrhagia was the most common presentation and the most common location was intramural. Degenerative changes were observed in 48.27% cases, amongst which hyaline change was the most common. The histologic variants which posed diagnostic difficulties were Cellular leiomyoma, Atypical Leiomyoma and Intravascular leiomyoma.

Conclusion: Uterine Leiomyomas are common benign tumors followed by their changes and variants, which can create diagnostic problems especially those with increased mitosis, cellularity and nuclear atypia.

Keywords: Leiomyoma; Variants; Changes.

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Introduction

Leiomyoma synonymously called as fibromyomas, vfibroids or myomas is the commonest visceral neoplasm affecting females in reproductive age group [1,2,3]. They are remarkably common with estimates of their frequency in hysterectomy specimen following careful histopathological examination as high as 77% (regardless of the reason for surgery) [4]. Most leiomyomas are asymptomatic in presentation and the other associated clinical symptoms include abnormal uterine bleeding, pelvic pain, pressure and infertility. Risk factors include race and parity with black and nulliparous women more likely to be affected. There exists many secondary changes as well as recognised histologic variants of a leiomyoma, some of which pose diagnostic problems in differentiating from malignant neoplasm like Leiomyosarcoma. The present study is undertaken, to study and analyze various histopathological changes within uterine leiomyomas in hysterectomy and myomectomy specimens.

Materials and Methods

The present study was conducted in the department of Pathology, AJ institute of medical sciences and research centre, Mangalore over a period of 2 years from May 2015 to April 2017. All hysterectomy and myomectomy specimens accounting for 420 specimen were retrieved and analyzed, out of which 348 cases diagnosed with leiomyomas were included in this study. Brief demographic and clinical data of patients were collected.

On receipt of surgical specimens they were properly labelled and numbered. These were fixed in 10% neutral buffered formalin for 24-48 hours. A detailed gross examination was made with reference to its location, size, appearance and secondary changes. Multiple sections were taken from representative areas, processed and paraffin blocks were made. The blocks were sectioned and stained routinely with hematoxylin and eosin stains. Histological features were extensively studied which includes cellularity, degenerative changes, cytologic atypia, mitotic rate, variation from usual morphology, necrosis, intravascular invasion.

Results

The study included 420 specimens (hysterectomy & myomectomy) in which 348 cases of uterine leiomyoma were identified. This accounts for 82.8% of all the cases studied pertaining to the uterus. Leiomyomas occurred mostly

in multiparous women (93.2%) compared to nulliparous women (6.8%). In the present study, patients with leiomyomas were aged between 22-77 years with peak incidence in the 4th decade of life with 150 cases followed by 116 cases in the third decade of life which accounted for 44.8% and 33.3% respectively. Age group of leiomyoma cases depicted in Table 1. Menorrhagia was the commonest clinical manifestation constituting 47.1% of cases, followed by pain abdomen (30.5%), dysmenorrhea (11.8%), mass per abdomen (7.5%), bladder disturbances (2%), primary infertility (1.1%). The most common site of leiomyomas was intramural (63.5%) followed by subserosal (29.3%) and submucosal leiomyoma (7.2%). Leiomyoma of usual histology having uniform cigar shaped nuclei arranged in intersecting and interlacing bundles of smooth muscle cells separated by variable amount of collagen accounts for 180 (51.7%) cases. Degenerative changes were observed in 168 (48.3%) cases, amongst which hyaline change was the most common with 138 cases (82.1%). Other secondary changes observed were cystic change 7 cases (4.2%), myxoid change 11 cases (6.5%), calcification 6 cases (3.6%), red degeneration 3 cases (1.8%) hydropic change 3 cases (1.8%) respectively. Degenerative changes in leiomyomas depicted in Table 2.

Table 1: Age group

Age Range (In Years)	No of Cases	Percentage
Below 20	0	0
21 - 30	18	5.3%
31 - 40	116	33.3%
41 - 50	156	44.8%
51 - 60	46	13.2%
Above 60	12	3.4%
Total	348	100%

Certain morphological variants of leiomyomas were encountered in the present study which require special mention-Atypical Leiomyoma, Cellular leiomyoma and Intravascular leiomyoma. 10 cases of variants of leiomyomas were observed which accounts for 2.8% of the cases which includes 7 cases of cellular leiomyoma, 2 cases of atypical leiomyoma and 1 rare case of intravascular leiomyoma.

Table 2: Degenerative changes

Secondary Changes	No of Cases	Percentage
Absent	180	51.7%
Present	168	48.3%

Hyalinization	138	82.1%
Cystic Change	7	4.2%
Myxoid Change	11	6.5%
Red Degeneration	3	1.8%
Calcification	6	3.6%
Hydropic Change	3	1.8%

Discussion

Uterine leiomyomas are benign smooth muscle tumor which are a major cause of morbidity in perimenopausal women [3]. They need hormonal milieu for their growth and maintenance. Estrogen and progesterone are implicated in the growth of a leiomyoma. Growth factors with mitogenic activity such as transforming growth factor Beta 3, basic fibroblast growth factor, epidermal growth factor and insulin like growth factor 1 are found to be elevated in leiomyomas and may be the effects of estrogen and progesterone [5]. The present study tries to analyze the morphology of uterine leiomyomas with regards to their manifestation, site, secondary changes and variants and to compare our findings with these of other similar studies from different parts of the world. Most subtypes of leiomyomas are chiefly of interest in that they mimic malignancy in one or more respects. These subtypes are mitotically active leiomyomas, cellular leiomyoma, atypical leiomyoma, intravascular leiomyoma. The ages of patients ranged from 22-77 years. Highest number of patients observed in the study were between 41-50 years with 150 (44.8%) cases. This was similar to studies by Lahori M et al. with 46.82%, Gupta et al. with 51.40%, Rizvi et al. with 45.56% [2,6,7]. Multiparous women (93.1%) were found to have leiomyomas more frequently than nulliparous (6.8%) in the present study analogous to study by Begum S et al. [8]. According to most studies uterine leiomyomas tend to be asymptomatic, but if symptomatic the most common clinical presentation noted is menorrhagia due to increased vascularity, increased endometrial surface and altered uterine contractility [3]. In the present study menorrhagia (47.1%) was the commonest presenting symptom followed by pain abdomen (30.5%). Menorrhagia was also the commonest presenting complaint in studies by Manjula K et al, Gowri et al., Lahori M et al., Abraham et al. [1,2,5,9].

The most common site of leiomyomas in the present study was intramural (63.5%) followed by subserosal leiomyomas (29.3%). Figure 1 depicts gross appearance of an intramural leiomyoma. This is in concordance with studies by Gowri et al., Lahori M et al., Manjula K et al., Geethamala et al. [1,2,3,9].



Fig 1: Intramural leiomyoma

In the present study secondary degenerative changes were noted in 48.3% of cases. The type of secondary change in a leiomyoma depend on the rapidity and degree of vascular insufficiency which may result in hyalinization, most common change, followed by cystic change, hemorrhage, hydropic change, myxoid change, calcification and very rarely malignant transformation or Leiomyosarcoma. Hyaline change (82.1%) constituted the commonest secondary change in the present study as well as studies by Lahori M et al., Manjula K et al., Abraham et al., Gowri et al. [1,2,5,9]. The microscopic appearance of hyaline change in a leiomyoma depicted in Figure 4. Other secondary changes noted in the present study were myxoid change (depicted in Fig. 10), cystic change, red degeneration (illustrated in Fig. 2), hydropic change and calcification. These secondary changes usually occur in long standing mature lesions and hence careful sampling should be done to rule out malignancy. Red degeneration occurs predominantly during pregnancy.



Fig 2: Leiomyoma with red degeneration

Specific morphological variants of leiomyomas though benign in nature need special mention as they can mimic malignancy or has metastatic potential. In the present study 10 cases of variant leiomyoma were seen. These included 7 cases of Cellular leiomyoma, 2 cases of Atypical leiomyoma and 1 case of Intravascular leiomyoma. Leiomyoma with increased cellularity, mitosis and nuclear atypia have to be differentiated from malignant tumors. Leiomyosarcoma, a malignant tumor showing smooth muscle differentiation is characterised by increased cellularity, mitosis greater than 10 per 10 HPF, diffuse nuclear atypia and coagulative necrosis [5].

Cellular leiomyoma according to WHO definition is one in which the cellularity is significantly greater than the surrounding myometrium [5]. They lack tumor cell necrosis and moderate to severe atypia and have infrequent mitosis [5,6]. All the 7 cases of cellular leiomyoma showed increased cellularity and few mitosis with no nuclear atypia and absence of necrosis with presence of large thick walled muscular vessels. The microscopic appearance of Cellular leiomyoma depicted in Figure 8. Cellular leiomyoma was found to be the most common variant in our study. Studies by Lahori et al and Abraham et al showed cellular variant to be the commonest variant, while study by Manjula et al. showed Lipoleiomyoma as the commonest variant.[2,5,9].

In the present study 2 cases of atypical leiomyoma were seen. It is a leiomyoma that exhibits moderate to severe cytologic atypia with enlarged hyperchromatic nuclei with prominent chromatin clumping, large cytoplasmic pseudo nuclear inclusions and multinucleated tumorgiant cells. It is otherwise known as "Bizarre" or "Symplastic Leiomyoma". This variant can be differentiated from malignancy by the absence of coagulative necrosis and mitotic count which is less than 10 MF/10 HPF. The histologic appearance of an atypical leiomyoma depicted in Figure 9.

Another extremely rare variant encountered in our study was one case of Intravascular leiomyoma of the uterus. The gross appearance of intravascular leiomyoma depicted in Figure 3. It is defined as an extension of grossly visible smooth muscle into vascular spaces or growth of microscopic tongues of benign smooth muscle cells into vessels beyond the confines of a leiomyoma [10]. Despite its cytohistological benignity, intravascular leiomyoma has metastatic potential because of vascular invasion. Most of the tumor arise in the uterus and grow into the lumen of uterine veins

but some may extend through the pelvic or ovarian veins into the inferior vena cava and reach the right side of the heart [10]. In general, intravascular leiomyomata affect premenopausal women, and the majority are parous [11]. It is unclear whether they form an extension from the uterine leiomyomas or their origin is primarily from the vessel wall itself [12]. The significance of this variant is that it can extend into the heart and cause mechanical obstruction leading to right sided heart failure. This is easily overlooked and maybe found incidentally during a surgery. A definitive intravascular leiomyoma diagnosis is confirmed by a histopathological analysis. The histological appearance of Intravascular leiomyoma depicted in Figure 5,6,7. Ovali and Cagler et al. reported 2 cases of intravascular leiomyoma in their study [10]. Nogales et al. in a series of 7 cases of Intravascular leiomyoma, suggested that the origin of IVL occurred from a pre-existing leiomyoma [12].



Fig. 3: Intravascular leiomyoma

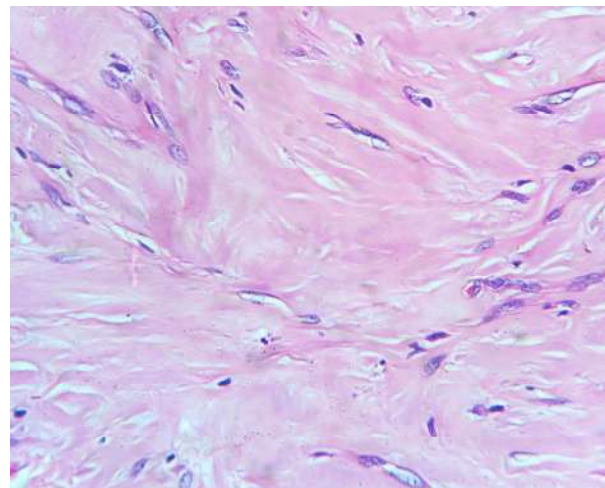


Fig. 4: Leiomyoma with hyaline degeneration (H & E x400)

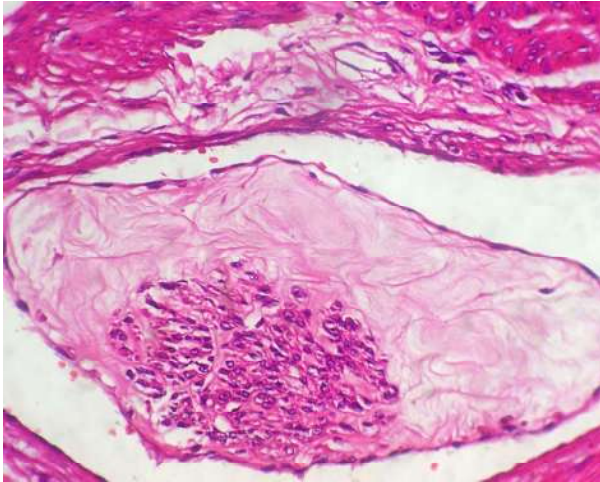


Fig 5: Intravascular leiomyoma-Leiomyoma within blood vessel (H&E x400)

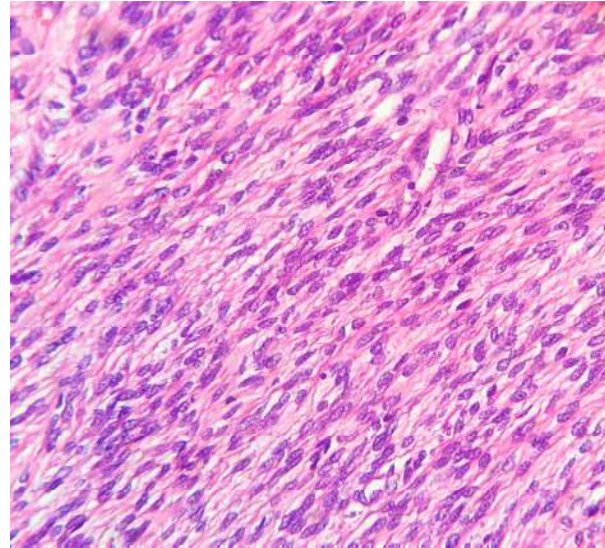


Fig 8: Cellular Leiomyoma (H & E x400)

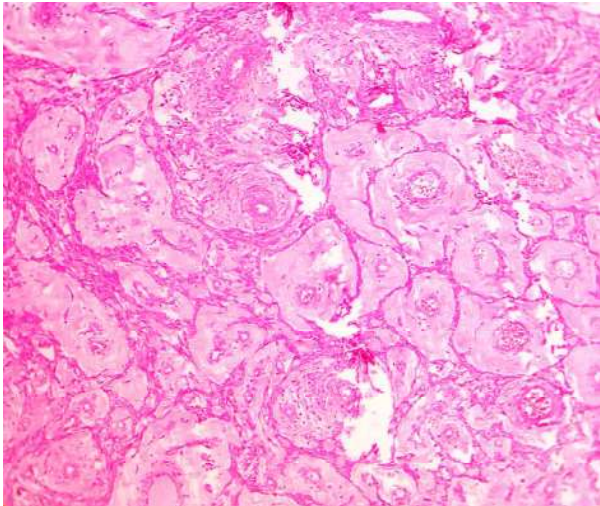


Fig 6: Intravascular leiomyoma-Leiomyoma with cord like pattern and multiple vessels with perivascular hyaline change (H&E x100)

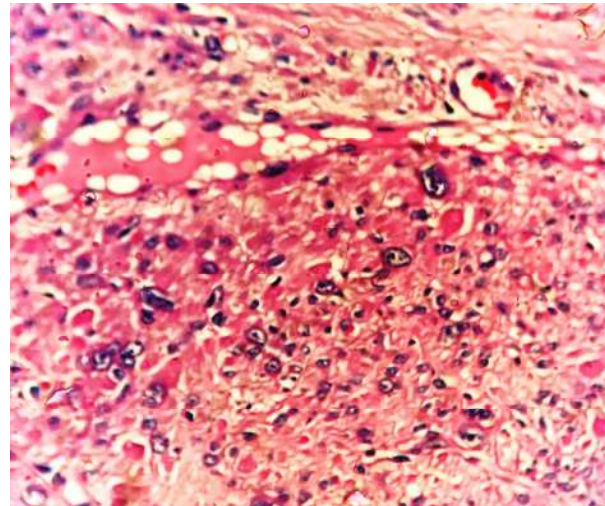


Fig 9: Atypical Leiomyoma (H & E x400)

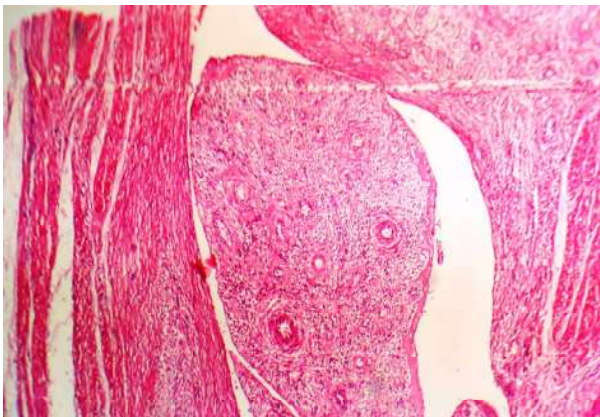


Fig 7: Intravascular leiomyoma-Leiomyoma within endothelium lined spaces (H&E x100)

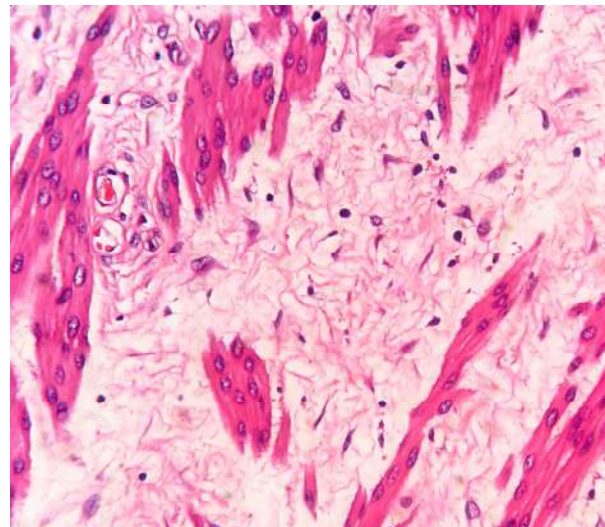


Fig 10: Leiomyoma with myxoid change (H & E x400)

Conclusion

Leiomyomata are the most common uterine neoplasms seen in women in the reproductive age group. They arise from the smooth muscle cells of the myometrium. The most common site is intramural for a uterine leiomyoma. Uterine leiomyomata exhibit various secondary changes of which hyaline degeneration is the commonest change. Special emphasis has been given to the rare variant, Intravascular leiomyoma as it is life threatening due to its metastatic potential and is often overlooked in clinical practice. Morphological variants and secondary changes of leiomyomas are relatively common, creating diagnostic problems especially those with increased cellularity, increased mitosis and nuclear atypia.

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