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Research Article

Morphological variants and secondary changes in uterine leiomyomas – Is it important to recognize them?

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Abstract

Background: Uterine leiomyomas are common tumours of the female genital tract and may be responsible for significant morbidity. These tumours are benign, but some of the variants and secondary changes may create diagnostic difficulties.

Objectives: This study was conducted to identify the secondary changes and variants of leiomyomas, especially those mimicking malignancy and to assess the histopathological features which help to differentiate them from malignant tumours.

Method: Hysterectomy and myomectomy specimens received over a period of two years were studied. Detailed gross and microscopic examination of the leiomyomas was done.

Results: 200 specimens (hysterectomy and myomectomy) were studied in which 545 leiomyomas were examined (seedling leiomyomas were excluded). Ages of patients ranged from 20 years to 72 years with peak incidence in the 4th decade. Secondary changes were observed in 24.2% cases and histological variants comprised 7.5% of the cases. The 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.

Conclusion: Uterine leiomyomas are common benign tumours in gynaecological histopathology specimens. However, secondary changes and morphological variants especially those with increased cellularity, increased mitoses and nuclear atypia create diagnostic problems. A thorough examination and adherence to the standard diagnostic criteria is required to rule out malignancy.

Keywords: uterine leiomyoma, variants, secondary changes, cellular leiomyoma, atypical leiomyoma, lipoleiomyoma

1. Introduction

Leiomyomas are benign smooth muscle tumours and are the most common benign solid tumours in women with an estimated incidence of 70% in hysterectomy specimens for noncancer – related conditions.[1] They occur in 20 – 25% of women over the age of 30 years.[2] Regardless of their benign nature, they can cause major problems clinically with menorrhagia being the most common presenting symptom followed by dysmenorrhoea, abdominal pain, mass and pressure symptoms. Infertility and repeated miscarriages are also reported.[3] There are many secondary changes as well as recognized histological variants of leiomyomas, some of which pose diagnostic problems in differentiating from malignant neoplasms like leiomyosarcoma (LMS). This study was conducted to identify the secondary changes and variants of leiomyomas, especially those mimicking malignancy and to assess the features of these which help to differentiate them from malignant tumours.

2. Material and Method

This is a prospective study done over a period of two years from May 2011 to April 2013. The patients' demographic data and detailed clinical history were recorded. The surgical specimens were allowed to fix in 10% formalin for 24-48 hours. Gross examination of the leiomyoma included location, number, size and secondary changes.

The tissue bits from representative areas were taken for histopathological examination and paraffin blocks were prepared. The number of blocks prepared depended upon the size and morphology of the tumours. Five micron thick sections were cut and stained with the routine haematoxylin and eosin stain. The histologic features that were studied and recorded included the degree of cellularity, crowding and overlapping of nuclei, nuclear atypia, mitoses (per 10 HPF), coagulative necrosis, presence of other secondary changes and variations in morphology and growth pattern.

3. Results

There were 710 hysterectomy and 27 myomectomy specimens received in the Department of Pathology during this period. Of these, 200 consecutive cases with leiomyomas were selected for the study. The total number of leiomyomas that were studied was 545. Seedling leiomyomas (less than 1cm) were not included in the study. The age of the patients ranged from 20 to 72 years. Majority of the patients (46.5%) were between 41-50 years.

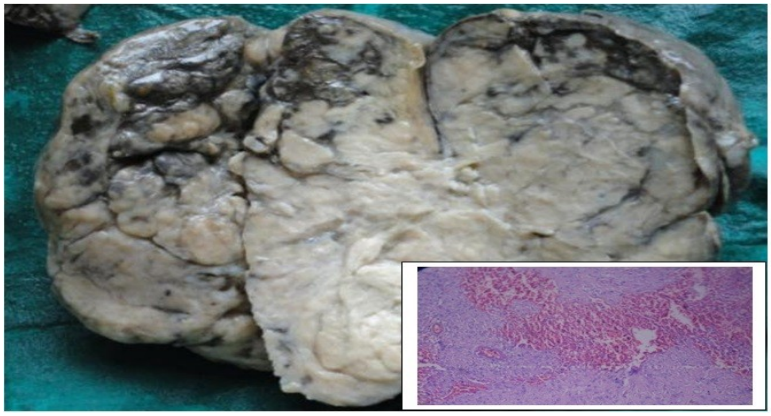
Most (88.5%) of the patients were mulitparous, with parity of two or more. The commonest clinical symptom in the present study was menorrhagia in 80 cases (40%) followed by dysmenorrhea in 62 patients (31%) and abdominal pain in 11 cases (5.5%). There were 11 patients (5.5%) who presented with primary infertility.

Eighty five cases (42.5%) had a solitary leiomyoma and 115 cases (57.5%) had more than one leiomyoma. Of these, 123 leiomyomas were purely intramural (61.5%) followed by 18 cases (9%) of subserosal leiomyomas and 10 cases (5%) cases of submucosal leiomyomas. Fifty cases (25%) had leiomyomas in more than one location of which intramural and subserosal were most common comprising of 38 cases (19%).

Histologically, 383 leiomyomas (70.3%) were leiomyomas of usual histology having bland, uniform, cigar shaped nuclei arranged in interlacing bundles with finely dispersed nuclear chromatin and separated by variable amounts of collagen.

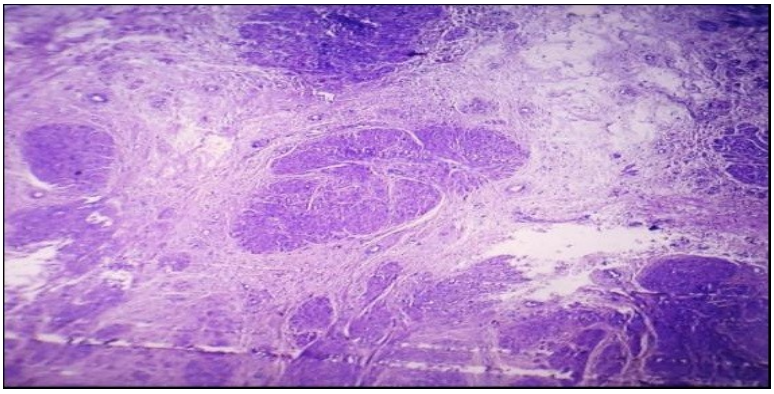
Secondary changes were observed in 121 leiomyomas (22.2%). Among these, 98 leiomyomas (49%) showed predominantly hyaline change and remaining 23 leiomyomas were associated with other secondary changes including 4 cases with hemorrhagic infarction (also called apoplectic leiomyoma or formerly as leiomyoma with red degeneration) (Figure 1), myxoid change (6 cases), hydropic change (1 case), perinodular hydropic change (1 case) (Figure 2), calcification (6 cases), cystic change (1 case), surface ulceration (1 case), haemorrhage (1 case), and with foci of mixed inflammatory cell infiltration (2 cases).

Figure 1: Cut surface of leiomyoma showing haemorrhagic infarction appearing as dark areas. Inset shows microscopic appearance (H&E x100).



Forty one cases of variants of leiomyomas were encountered constituting 7.5% of the cases, which included 32 cellular leiomyomas (Figure 3), 4 lipoleiomyomas, 2 cases with lymphoid infiltration, 2 cases of bizarre (symplastic) leiomyomas and 1 case of epithelioid leiomyoma. These secondary changes and variants were found in the leiomyomas irrespective of their location.

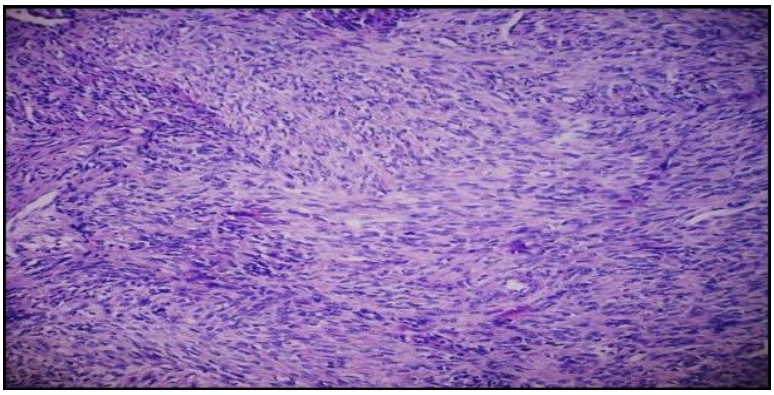
Figure 2: Leiomyoma with perinodular hydropic change showing nodules of smooth muscle cells surrounded by oedematous material. (H&Ex100)



In this study, there were 32 cases of cellular leiomyomas and thirty one patients were in the age group of 31- 50 years. All the patients presented with clinical features of menorrhagia and dysmenorrhea. The tumour size ranged from 2 to 9 cms. There was no specific location observed. Histology showed increased cellularity with the smooth muscle cells being spindle shaped, closely packed with some showing overlapping, and scant mitotic figures (<1/10HPF). The uniformity of the cells, scanty mitoses and absence of necrosis helped to exclude LMS.

Four cases of lipoleiomyomas were encountered in this study with age ranging from 32 to 56 years. The patients presented with abdominal pain, excessive bleeding and dysmenorrhea. The tumours were large and measured 5.5 to 25 cms in diameter. Three tumours were intramural and 1 submucosal in location. Histology showed admixture of varying amounts of mature adipose tissue with smooth muscle cells.

Figure 3: Cellular leiomyoma showing increased cellularity but lacking nuclear atypia and with scanty mitoses. (H&E x100)



There were 6 patients with myxoid change. The age range was from 31 to 54 years and clinical features were abdominal pain and menorrhagia. The tumours measured 5 to 20 cms in diameter. Four tumours were situated intramurally and two were subserosal in location. Cut surface showed grey white whorled appearance with myxoid areas. Microscopy showed elongated uniform spindle cells suspended in abundant myxoid material.

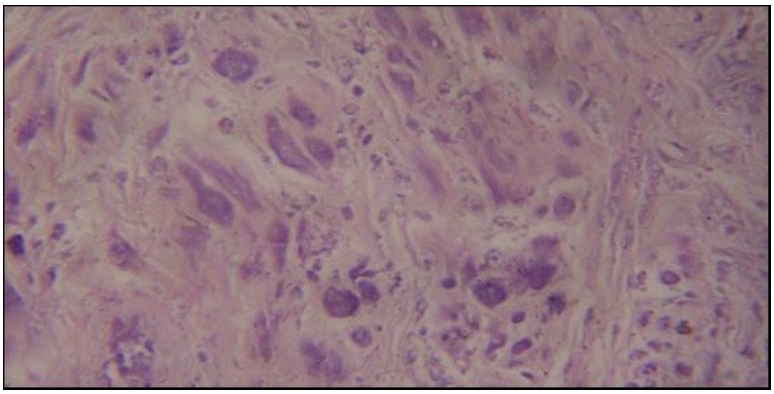
One case in a 41 year old patient, there was extensive perinodular accumulation of fluid which was designated as perinodular hydropic leiomyoma. The tumour size was 6x6cms. Microscopy showed typical leiomyomatous areas separated by oedema in a perinodular pattern. Myxoid LMS was ruled out in both the cases by the absence of pleomorphism, mitoses and necrosis.

There were 2 cases of leiomyoma with lymphoid infiltration diagnosed in 37 and 45 years old patients, both of whom presented with menorrhagia. Both tumours were located intramurally and both measured 7 cms in diameter.

Microscopically, numerous small lymphocytes were seen admixed with plasma cells and eosinophils, with the lymphoid infiltrate clearly confined to the leiomyomas.

A case of epithelioid leiomyoma was diagnosed in a 37 years old patient who presented with menorrhagia since 8 months. The tumour measured 5x3 cm in size and was intramural in location. On cut section the tumour was well circumscribed and showed characteristic grey white whorled appearance. Microscopy consisted of predominantly round to polygonal cells having abundant acidophilic to clear cytoplasm. The nuclei were round and centrally placed. There was no nuclear pleomorphism, mitoses and necrosis which helped to rule out an epithelioid LMS.

Figure 4: Photomicrograph of atypical leiomyoma showing irregularly shaped bizarre cells with hyperchromatic large nuclei and a multinucleated giant cell (H&E x400)



In this study, two cases of bizarre leiomyoma (Figure 4) were diagnosed in two patients who were 30 and 36 year old. They presented with abdominal distension. Grossly the tumours measured 2cms and 4cms respectively and were intramural and subserosal in location. Microscopically, the tumours were cellular and showed 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 LMS.

4. Discussion

Uterine leiomyomas are benign neoplasms commonly encountered in gynaecological practice. Estrogen and progesterone are recognized as promoters of tumor growth, and the potential role of environmental estrogens has only recently been explored. Growth factors with mitogenic activity, such as transforming growth factor-β3, basic fibroblast growth factor, epidermal growth factor, and insulin-like growth factor-I, are found to be elevated in leiomyomas and may be the effectors of estrogen and progesterone promotion. Nonrandom cytogenetic abnormalities have been found in about 40% of tumors examined. One of the most common of these is a translocation between chromosomes12 and 14, specifically t(12;14) (q14-q15;q23- q24), which is present in about 20% of karyotypically abnormal leiomyomas. Another frequently encountered karyotypic abnormality in fibroids is a deletion of chromosome 7, del(7)(q22q32), which is present in about 17% of karyotypically abnormal leiomyomas. A third cytogenetic subgroup consists of aberrations of 6p21, including deletions, inversions, translocations, and insertions. Trisomy 12 has been reported in as many as 12% of karyotypically abnormal leiomyomas.[4]

Several secondary changes and histological variants of uterine smooth muscle tumours have been identified. Secondary changes occurring in leiomyomas are detectable in approximately 65% of cases. These include hyaline change, mucoid, myxoid or myxomatous change, calcification, cystic changes and fatty metamorphosis.[3] Histological variants include, cellular leiomyoma, apoplectic leiomyoma, leiomyoma with lymphoid infiltration, atypical (bizarre, symplastic or pleomorphic) leiomyoma, lipoleiomyoma, palisaded leiomyoma, epithelioid (clear cell) leiomyoma, cotyledonoid dissecting leiomyoma, parasitic leiomyoma, leiomyoma with skeletal muscle differentiation, diffuse leiomyomatosis, intravenous leiomyomatosis, benign metastasizing leiomyoma and mitotically active leiomyoma.[3] The incidence of these changes and variants are similar to other publications where a large number leiomyomas were studied.[5, 6, 7, 8]

Hyaline change and calcification are usually seen in long standing leiomyomas and do not pose significant

diagnostic problems.

Leiomyomas with increased cellularity, mitoses and nuclear atypia have to be differentiated from malignant tumours. LMS, a malignant tumour showing smooth muscle differentiation is characterised by increased cellularity, mitoses greater than 10 per 10 high power fields (HPF), diffuse nuclear atypia and coagulative necrosis.[3] Smooth muscle tumour of uncertain malignant potential (STUMP) is defined by World Health Organization (WHO) as a smooth muscle tumour which cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria.[2]

Cellular leiomyomas are defined by the WHO as a leiomyoma having cellularity which is significantly greater than that of the surrounding myometrium.[1] They lack tumour necrosis and moderate to severe atypia, and have infrequent mitoses.[1,2,5,9,10] 'Highly cellular leiomyoma' have been recently defined as a distinct entity. Those without significant atypia, necrosis or high mitotic count carry a good prognosis similar to the usual leiomyoma.[11] Mitotically active leiomyoma refers to tumours having 5-15 mitoses/10 HPFs but lacking necrosis or cytological atypia. The clinical behaviour is like that of a benign neoplasm.[2, 3, 11]

In the absence of objective criteria for definition of cellularity, there is need for additional markers to differentiate from STUMP and LMS. The benign uterine smooth muscle tumours express receptors to the two hormones, estrogen and progesterone. LMS show reduced Estrogen Receptor (ER) & Progesterone Receptor (PR) expression suggesting an abnormal expression of the ovarian steroid receptors. This finding could be helpful in differentiating benign from malignant tumours.[12, 13, 14] In all our cases of cellular leiomyomas, there was only increased cellularity and few mitotic figures, with absence of necrosis and nuclear atypia.

Highly cellular leiomyoma shows cellularity which is as great as that of typical endometrial stromal tumours. These are commonly confused with either stromal nodules or low grade endometrial stromal sarcomas. Helpful features in the differential diagnosis are coexistence of the highly cellular areas with a fascicular growth pattern typical of smooth muscle tumours, reticulin fibres that tend to parallel the fascicles of cells in leiomyomas but surround individual tumour cells in endometrial stromal tumours and vessels of large calibre with thick muscular walls; in contrast to the prominent network of small blood vessels typical of endometrial stromal tumours. Immunoreactivity for desmin is also helpful in differentiating cellular and highly cellular leiomyomas from stromal tumours. Diffuse desmin immunoreactivity supports smooth muscle differentiation and focal immunoreactivity. In young women wishing to retain their fertility or in older women with high surgical risk it is very important to differentiate the two tumours.[1, 11, 15]

Atypical leiomyomas (bizarre, pleomorphic or symplastic leiomyoma) greatly mimics LMS. Microscopically, the defining feature of this tumour is the presence of bizarrely shaped multinucleated and multilobated giant cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm, prominent nuclear pseudoinclusions, and atypical nuclei distributed throughout the tumour. Typically, the areas uninvolved by the bizarre cells show bland cytologic features. Most important clue in differentiating bizarre leiomyoma from a malignant tumour is the patchy or multifocal distribution of bizarre cells in the tumour. Other helpful features are low mitotic activity and absence of tumour cell necrosis. Ancillary techniques, such as ploidy, MIB-1 and p53 expression are useful. [2, 11, 15] The two cases in our study, which were seen in myomectomy specimens in younger females showed only nuclear atypia without necrosis or significant mitoses and hence were diagnosed as atypical leiomyoma.

Epithelioid leiomyomas are composed of epithelial-like cells. They are rare and criteria predictive of their malignant behaviour are less well established than that for spindle-cell smooth muscle tumours. Small size, circumscribed margin, presence of clear cytoplasm, extensive hyalinization, and lack of necrosis are parameters associated with a favourable prognosis; whereas those with two or more of the following criteria like larger size (>6 cm), those that exhibit 2-4 mitotic figures/10 HPFs, moderate to severe atypia and necrosis should be classified as those with uncertain malignant potential. Frankly malignant tumours are designated epithelioid leiomyosarcoma. [2, 11] The case of epithelioid leiomyoma in our study showed epithelioid cells but no necrosis or mitoses.

Myxoid leiomyoma is composed of benign smooth muscle cells with myxoid material separating the tumour cells. The margins are circumscribed and neither cytological atypia nor mitotic figures are present. Large myxoid smooth muscle tumours and those with an infiltrating margin, moderate to severe nuclear atypia, with or without necrosis and any mitotic index, should be regarded myxoid leiomyosarcomas. [2, 11, 15]

Hydropic change refers to the accumulation of abundant oedematous fluid, which is a common focal finding on

gross and microscopic examination of otherwise typical leiomyomas. It is often associated with hyalinisation. Hydropic degeneration can sometimes cause significant diagnostic confusion, in particular when it occurs in a perinodular distribution referred to as perinodular hydropic leiomyomas. This can, in some cases, be confused with intravascular leiomyomatosis or myxoid leiomyosarcoma because of hydropic change extending beyond the confines of leiomyoma.[1,15] The cases of myxoid leiomyoma and perinodular hydropic change in our study, had no features suggestive of malignancy and therefore, there was no difficulty in designating them as benign.

Apoplectic leiomyoma or leiomyoma showing hemorrhagic infarction, commonly called red degeneration, refers to tumour with dark red gross appearance. Histological examination shows extensive infarction sometimes with surviving marginal zone of benign smooth muscle cells showing mitoses. Nuclear atypia is absent.[1,2,11] Occasionally, nucleomegaly and prominent nucleoli can be seen.[10] Haemorrhagic infarction is a rare event, but when it occurs, it is reported more often during pregnancy as an acute clinical presentation.[1,2,11] It is also reported during the postpartum period and in women taking oral contraceptives.[2,3,11] It is important to recognise this change to avoid misdiagnosing the tumour as malignant.[1,2,11] One of the tumours in our study showed nuclear atypia without any mitoses or tumour necrosis and was considered benign.

Lipoleiomyomas are uncommon and their reported incidence varies from 0.03 to 0.2% and show histological features of admixture of varying amounts of mature adipose tissue with smooth muscle cells.[4,16,17] The differential diagnoses of similar uterine tumours with adipose tissue and spindle cells include spindle cell lipoma, angiolipoma, angiomyolipoma, leiomyoma with fatty degeneration, atypical lipoma, and well differentiated liposarcoma.[15] The frequency of lipoleiomyoma in our study was slightly higher (0.7%) than reported in other studies.

Uterine leiomyomas with massive lymphoid infiltration is a rare and unusual pathological finding with only 20 cases having been reported in the literature. The main differential diagnosis is from a malignant lymphoma and inflammatory pseudotumour. Leiomyoma with lymphoid infiltration, on gross examination, resembles typical leiomyomas. 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.[15,18]

In conclusion, uterine leiomyomas are common tumours in gynaecological histopathology specimens. Secondary changes and variations in morphology especially increased cellularity, increased mitoses and nuclear atypia create diagnostic problems. A detailed examination and adherence to the diagnostic criteria are required to rule out malignancy.

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