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**Research Article**

# EXPRESSION OF Ki-67 IN UTERINE SMOOTH MUSCLE TUMORS AS A PREDICTOR OF PROLIFERATIVE ACTIVITY

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**A R T I C L E I N F O**

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**A B S T R A C T**

**Context**: Uterine smooth muscle tumors comprise of benign leiomyomas, benign variants of leiomyomas, borderline neoplasms and malignant leiomyosarcomas. Accurate categorization of these tumors by light microscopy can be challenging, particularly the distinction of leiomyosarcomas from certain benign variants and tumors of uncertain malignant potential.

**Objective**: The aim of the current study was to evaluate the expression of Ki-67 in uterine smooth muscle tumors, comparing leiomyomas, leiomyoma variants and leiomyosarcomas (LMS) and to prove the accuracy of ki-67 expression as a useful parameter in the diagnosis of these neoplasms.

**Study design**: In our study, we analysed 230 cases of uterine smooth muscle tumors histopathologically and 50 cases were selected for assessment of ki-67 expression, using immunohistochemistry. Ki-67 expression was then correlated with the histopathological diagnosis.

**Results**: Our results demonstrated that there was significantly elevated ki-67 expression in leiomyosarcomas, which correlates well with the rapid growth of these malignant tumors, significantly low ki-67 expression in usual leiomyomas and intermediate level of expression in certain histopathologically benign variants.

**Conclusion:** Ki-67 may be a useful immunohistochemical parameter to distinguish between cases of malignant smooth muscle tumors from those with borderline histology or certain variants, with special concern towards their biological behavior.



## INTRODUCTION

Uterine smooth muscle neoplasms range from common benign leiomyomas to rare highly malignant leiomyosarcomas. They are classified as benign or malignant based upon histologic features. However, some of the variants have histologic findings that make it difficult to define them as benign or malignant (e.g, smooth muscle tumors of uncertain malignant potential, atypical leiomyoma).

Benign smooth muscle neoplasms (ie, leiomyomas of the usual histologic type or "garden-variety" leiomyomas) are defined as follows[1] : Low mitotic index (<5 mitoses per 10 high-power fields [HPF], no cytologic atypia, no cell necrosis (apart from bland degeneration due to tumor ischemia), spindle-shaped cells that are uniform in size and shape, no intravascular component and well-circumscribed mass. Leiomyoma of the uterus is the most frequent smooth muscle neoplasms with excellent clinical outcome. Leiomyosarcomas are rare, but clinically aggressive neoplasms with poor survival. Compared with other types of uterine cancers, they are aggressive associated with a high risk of recurrence and death, regardless of the stage at presentation[2]. The Stanford criteria for the histologic diagnosis of malignant smooth muscle tumors (leiomyosarcoma) reported by Bell *et al*., include at least two of the following criteria: diffuse moderate to severe atypia, a mitotic count of at least 10 mitotic figures/10 hpf and tumor cell necrosis[3].

Benign variants of uterine smooth muscle neoplasms are well recognized entities, though not very common. Clinically, they have favouable outcome, comparable to leiomyomas.

Mitotically active leiomyomas are typically small, well circumscribed, and almost always behave in a benign fashion[4,5]. These variants are defined by the isolated presence of one feature associated with a malignant neoplasm, which is increased proliferative activity. Specifically, they are leiomyomas with an increased mitotic count (≥5, but <15 mitoses per 10 high-powered fields [HPF] but lacking atypia or geographic tumor necrosis. Other variants are epithelioid leiomyoma, schwanommatous leiomyoma, myxoid leiomyoma etc. These are extremely rare entities and typically behave in a benign fashion.

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Neoplasms with uncertain clinical behavior includes smooth muscle tumors of uncertain malignant potential (STUMP), cellular leiomyoma and leiomyoma with bizarre nuclei (atypical/symplastic leiomyoma). They are most concerning in terms of progression or missed diagnosis of sarcoma.

Smooth muscle tumors of uncertain malignant potential are rare and thus the paucity of data makes it difficult to describe their clinical behavior. The term Smooth muscle tumors of uncertain malignant potential (STUMP) was firstly used in the literature by Kempson in 1973[6] and the current WHO classification indicates that a uterine smooth muscle tumor not diagnosed unequivocally as benign or malignant should be defined as STUMP[7]. STUMPs are known to show delayed recurrences. It is plausible that tumors defined as STUMPs may be variants of leiomyomas with unusual pathologic features. On the other hand, some tumors regarded as STUMPs may in reality be underdiagnosed leiomyosarcomas[8].

Leiomyoma with bizarre nuclei are neoplasms having focal, multifocal, or diffuse atypia .The atypia must be "significant" (moderate to severe in histologic terms); neoplasms with mild changes are not classified as atypical leiomyomas.

Cellular leiomyomas are defined as having significantly more cellularity than the surrounding myometrium. There is no discrete quantitative definition for hypercellularity, and application of the term varies somewhat across pathologists.
The classification of leiomyoma variants and distinction of borderline (STUMP) from malignant tumors is also important for the clinicians to decide upon an appropriate therapeutic plan, as they have different biological behaviours, as discussed above.

Because simple morphological evaluation based on hematoxylin and eosin-stained sections is an imperfect predictor of behaviour in some uterine smooth muscle tumors (especially certain leiomyoma variants), various ancillary techniques have been evaluated to improve diagnostic accuracy[9]. Proliferation marker ki-67 is one such tool that can be utilized in conjunction with histopathological examination to enhance the diagnostic accuracy in these problematic neoplasms. The fact that the Ki-67 protein is present during all active phases of the cell cycle (G(1), S, G(2), and mitosis), but is absent from resting cells (G(0)), makes it an excellent marker for determining the so-called growth fraction of a given cell population[10].

The present study was designed to evaluate the potential value of Ki-67 immunohistochemical marker in enhancing/supporting the histological findings of various types of uterine smooth muscle tumors with reference to their proliferative activity. In our study we included 230 cases of uterine smooth muscle tumors, diagnosed and subclassified histopathologically. Out of these, 50 cases were selected for ki-67 immunostaining.

While H&E remains the most important tool in diagnosing uterine smooth muscle tumors, Ki-67 can serve as adjunct for classification of equivocal lesions.

## MATERIALS AND METHODS

The present study was conducted at the Department of Pathology, GSVM Medical College Kanpur, from December 2010 to September 2012. The study consisted of hysterectomy and myomectomy specimens, received in the department during this period for histopathological examination.

Formalin fixed and paraffin embedded tissues were obtained from these specimens. All specimens were examined using H&E preparations. 230 cases were confirmed to be uterine smooth muscle tumors. On the basis of morphological parameters (cellularity, cytological atypia, tumor necrosis ) and mitotic index (mitotic figures/ hpf), the tumors were typed as usual leiomyomas, variants of leiomyomas, or leiomyosarcomas.

50 cases were selected for immunohistochemical staining with Ki-67, comprising of 24 cellular leiomyomas, 12 mitotically active leiomyomas, 4 atypical leiomyomas, 3 borderline tumors, 2 leiomyosarcomas and 5 usual leiomyomas for control.

***Immunohistochemistry***

1. Immuno histochemical staining was carried out using polymer labeling technique (Dako Envision).
2. Sections were dewaxed, washed in alcohol and antigen retrieval carried out in a Decloaking Chamber (Pascal) with 10 mM Citra solution at 125 degrees C for 30 seconds followed by 90 degrees C for 10 seconds.
3. Slides were cooled naturally and brought to room temperature.
4. Slides were placed inside the Dako Autostainer Universal Staining System (Automated Immunohistochemistry Staining System).
5. Endogenous peroxidase was blocked by using 0.3% hydrogen peroxide in methanol at room temperature for 10 min.
6. Slide were washed PBS (Phosphate Buffered Saline) briefly and incubated with primary antibody (Ki-67) for 60 mins.
7. Sections were washed with PBS and incubated with the polymer for 30 minutes.
8. Sections were washed with PBS. Diaminobenzidine (DAB) was used as the chromogen in hydrogen peroxide for 10 minutes.
9. Sections were then counterstained with haemotoxylin and mounted.

Criteria for positivism and negativism of cell nuclei were based on data, suggestions and photographs published in recent notebook of immunohistochemistry[11]. Every nucleus stained brown, regardless of shade intensivity, was considered positive. The interpretation of immunohistochemical staining was expressed as number of positive cells in 100 cell count in most active area of the slide, after counting 500 cells.

***Based on ki-67 expression, the cases were divided into various categories***

- Negative staining – No cell showing nuclear positivity.
- <5%
- 5-9%
- 10-14%
- 15-19%
- >20%

The ki-67 labelling index was then correlated with the histopathological diagnosis and subclassification.

## RESULTS

**Table 1** shows that majority 215/230 of them showed low mitotic count (<5/10hpf), 10/230 showed 5-10 mf/10hpf and only 5/230 showed > 10 mf/10hpf.

**Table 1** Mitotic Index

| Mitotic index | No. Of cases | Percentage |
|---|---|---|
| < 5/10 hpf | 215 | 93.5% |
| 5-10/10 hpf | 10 | 4.3% |
| >10/10 hpf | 05 | 2.2% |

It was observed that most of the uterine smooth muscle tumors ( 93.5%) showed a low mitotic activity.

Based on the mitotic index, cellularity, cytological atypia and presence/absence of tumor necrosis, the 230 cases were subclassified as usual leiomyomas, specific variants, borderline tumors and leiomyosarcomas (Table 2). Majority were usual leiomyomas (166/230). Leiomyosarcomas were the least common (2/230) (figure 5 and 6). 3/230 were found to be borderline tumors (figure 4) and rest (59/230) were benign variants of leiomyoma. Figure 1 shows mitotically active leiomyoma, figure 2 shows cellular leiomyoma and figure 3 shows atypical leiomyoma.

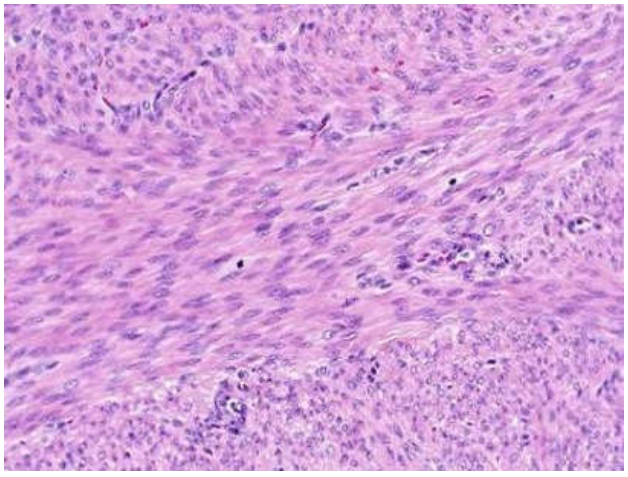


**Figure 1** mitotically
active leiomyoma here we see, several mitotic figures in the same field ( arrowheads ). in this case the mitotic count was >5 but < 15 / 10 hpf ( after counting in several areas ). no tumor necrosis or cytological atypia was found ( h&e, 40x).

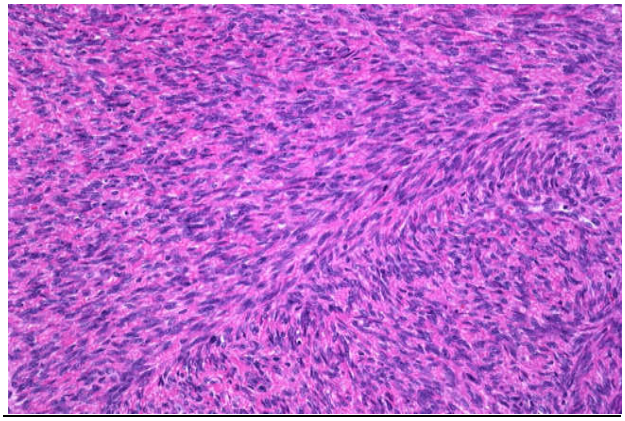


**Figure 2** cellular leiomyoma
Here we see, the cellularity is more than the normal myometrium, but lack nuclear atypia and tumor necrosis. Mitotic count was < 5/ 10 hpf in this case (calculated after counting in several areas) ( h&e, 40x)

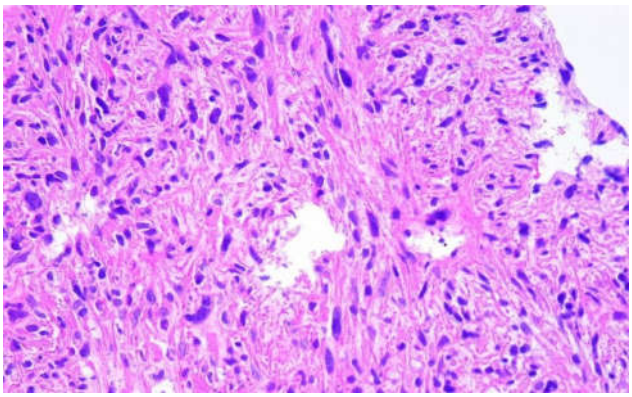


**Figure 3** Atypical Leiomyoma
Here we see atypical leiomyoma showing numerous bizarre nuclei in smooth muscle cells, but <10 mitotic figures/ 10 hpf ( after counting in several fields) and no tumor necrosis ( H&E, 40x).

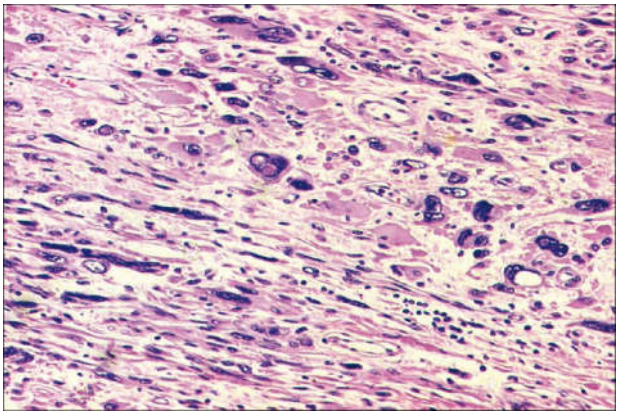


**Figure 4** Borderline Neoplasm

Here we see, marked cytological atypia in the upper area (black arrow) and moderate atypia in the lower area (red arrow). However, in this case after thorough searching in all the areas, no tumor necrosis was found and mitotic figures were > 10 but < 15 / 10 hpf.(H&E, 40x)

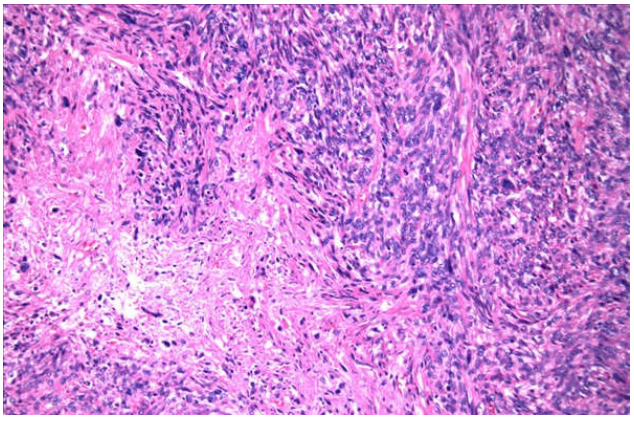
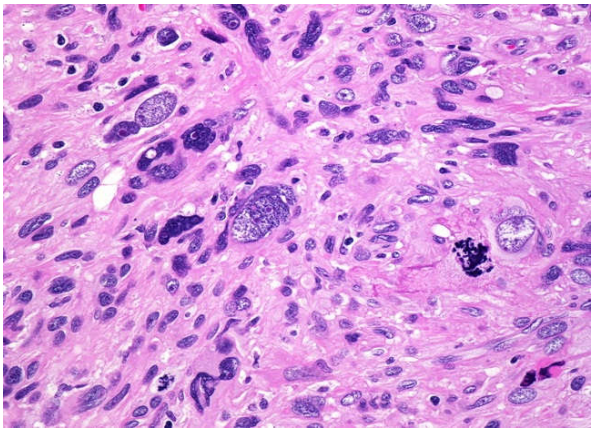


**Figure 5** Leiomyosarcoma

Here we see, typical geographic necrosis (double arrowhead ), hypercellularity , cytological atypia ( arrowhead ) and increased mitotic figures ( curved arrowhead ) (H&E, 40x).

Most (225/230) of these neoplasms were subclassified as benign leiomyomas and their benign variants, 3/230 were borderline and only 2/230 were malignant leiomyosarcomas (Table 3).

Ki-67 expression: The results in our study showed significant difference in Ki-67 expression between LM and STUMP as well as between LM and LMS (Table 4). Figure 7 shows variable ki-67 expression in these tumors.



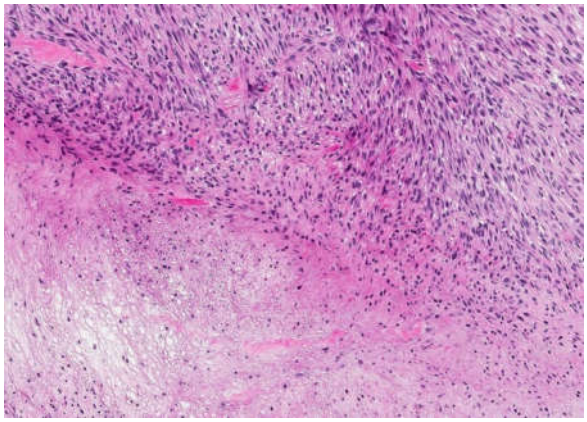


**Figure 6** Leiomyosarcoma
Here we see, focal marked cytological atypia (first figure, H&E,100x), increased mitotic figures and tumor necrosis in other area ( second figure,H&E, 40x )

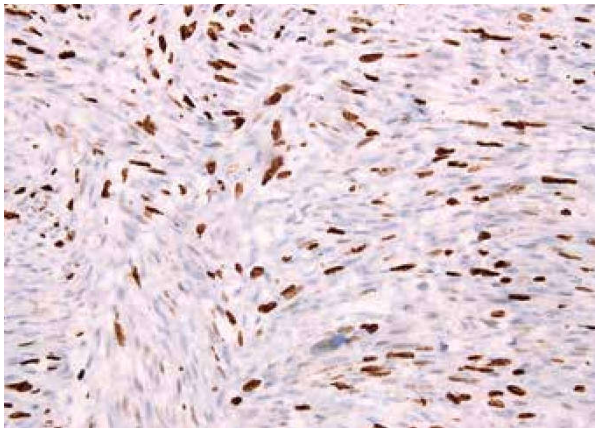
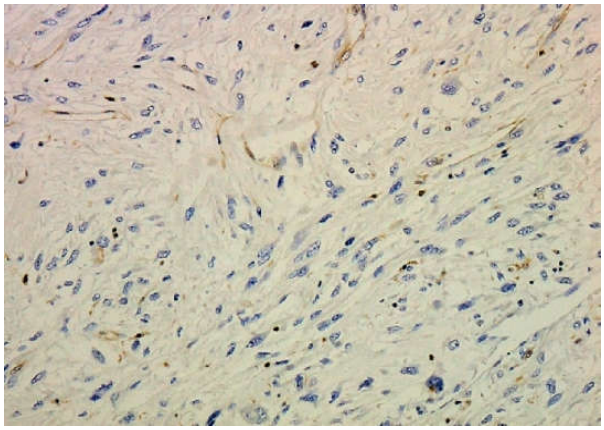
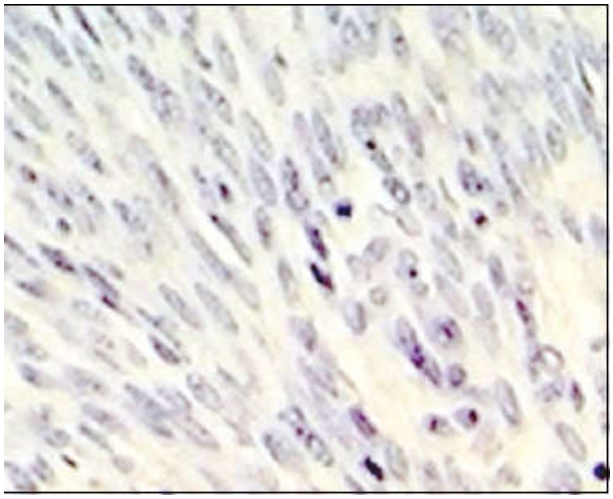


**Figure 7** ki-67 expressionLeiomyosarcoma
Here we see, ki-67 labelling index > 20% ( IHC ki-67, 40x ).



Borderline neoplasm (stump) Here we see, ki-67 labelling index 10-15% (ihc ki-67, 40x ).



**Leiomyoma**
Here we see, negative reaction in leiomyoma (IHC ki-67, 40x)

**Table2** histopathological subclassification on the basis of the calculated mitotic index and other morphological features, the uterine smooth muscle tumors were subclassified.

| Mitotic index | Cellularity | Nuclear atypia | Tumor necrosis | Morphological subtype | No.of cases |
|---|---|---|---|---|---|
| <5 PER 10 hpf | Normal | Absent | Absent | Usual leiomyoma | 166 |
| | | | | Epithelioid leiomyoma | 08 |
| | Increased | Absent | Absent | Schwanomatous leiomyoma | 11 |
| | | | | Cellular leiomyoma | 24 |
| | Normal | Marked, focal | Absent | Atypical leiomyoma | 04 |
| | Normal | Marked, diffuse | Absent | Borderline tumor | 02 |
| | Normal | Absent | Present | Borderline tumor | 01 |
| 5 -10 PER 10 hpf | Normal | Absent | Absent | Mitotically active leiomyoma | 10 |
| >10 PER 10 hpf | Normal | Absent | Absent | Mitotically active leiomyoma | 02 |
| | Increased | Present | Present | Leiomyosarcoma | 02 |
| Total | | | | | 230 |

It was observed that out of 230 cases, 166 were usual leiomyomas, 8 epithelioid leiomyomas, 11 schwanommatous leiomyomas, 24 cellular leiomyomas, 12 mitotically active leiomyomas, 4 atypical leiomyomas, 3 borderline neoplasm and 2 leiomyosarcomas.

**Table 3** Categorization Based On Histopathological Classification

| Category | No. Of cases | Percentage |
|---|---|---|
| Benign | 225 | 97.8% |
| Borderline | 03 | 1.3% |
| Malignant | 02 | 0.9% |

It was observed that most of the neoplasms were histopathologically benign, 3 were borderline and 2 were confirmed to be leiomyosarcomas.

**Table 4** Ki-67 EXPRESSION (% of cells with positive nuclear staining)
Out of 230 uterine smooth muscle tumors included in the study, 50 were selected for Ki-67 immunostaining, including 45 histologically benign, 03 histologically borderline and 02 histologically malignant. We categorized the percentage expression into <5%, 5-10%, 10-14%, 15-19% and >20%. 3 cases of usual leiomyomas show no ki-67 expression.

| Histopathology | No. Of cases | Ki-67 expression |
|---|---|---|
| Usual leiomyoma | 03 | No reactivity |
| Usual leiomyoma | 02 | <05 % |
| Cellular leiomyoma | 23 | <05 % |
| Cellular leiomyoma | 01 | 5-9 % |
| Mitotically active leiomyoma | 09 | 10-14% |
| Mitotically active leiomyoma | 03 | 5-9 % |
| Atypical leiomyoma | 04 | 5-9% |
| Borderline neoplasm | 02 | 10-14% |
| Borderline neoplasm | 01 | 15-19% |
| leiomyosarcoma | 02 | >20% |
| Total | **50** | |

It was observed that out of 50 cases, 3 cases did not show any ki-67 expression. Most of the benign variants showed <10% ki-67 positivity, except 9/12 cases of mitotically active leiomyomas which showed 10-14% ki-67 positivity. 2/3 Borderline tumors showed >10% ki-67 positivity and 1/3 borderline tumor showed 15-19% ki-67 positivity. Both cases of leiomyosarcomas showed >20% ki-67 positivity.

**Table 5** Analysis Of Ki-67 Expression With Respect To Their Histopathology

| Histopathological Category (no. Of cases/total) | Ki-67 labelling index | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | Negative | <5% | 5-9% | 10-14% | 15-19% | >20% | |
| Benign ( 45/30) | 03 | 25 | 08 | 09 | | | 45 |
| Borderline (03/30) | | | | O2 | 01 | | 03 |
| Malignant ( 02/30) | | | | | | 02 | 02 |
| **Total** | | | | | | | 50 |

***Following findings were observed***

- Out of 45 cases, diagnosed as benign uterine smooth muscle tumors on histopathology, majority (36) had Ki-67 labelling index < 10% and rest (09) had Ki-67 labelling index between 10-19%, but none had Ki-67 labelling index >20%.
- Out of 03 cases that were histopathologically diagnosed as borderline uterine smooth muscle tumors, 02 had Ki-67 labelling index 10-14 %, indicating relatively higher proliferative activity, as compared to their benign counterparts. 01 case had Ki-67 labelling index between 15-19%, indicating its high proliferation but still lesser than leiomyosarcomas.
- Both of the histopathologically diagnosed malignant uterine smooth muscle tumors, had Ki-67 labelling index more than 20%.

- 3/5 usual leiomyomas showed no nuclear staining. 2/5 of the *usual leiomyomas*, showed < 5% ki-67 expression.
- Most of the *cellular leiomyomas* (23/24) showed < 5% ki-67 expression. 1/24 showed 5-9% ki-67 expression.
- 9/12 *mitotically active leiomyomas* showed 10-14% ki-67 expression. 3/12 showed 5-9% expression.
- All of the *atypical leiomyomas* (4/4) showed 5-9% ki-67 expression.
- 2/3 of the *Borderline tumors* showed 10-14% ki-67 expression. 1/3 showed 15-19% expression.
- Both *Leiomyosarcomas* (2/2) showed >20% ki-67 expression.

## DISCUSSION

The results in our study showed that leiomyosarcomas clearly exceeded benign neoplasms (leiomyomas and variants) in expressing ki-67. Also borderline neoplasms showed much greater level of ki-67 expression as compared to the benign variants, but still lagged behind leiomyosarcomas in the same. Certain benign variants showed higher level of ki-67 compared to the usual leiomyomas, particularly mitotically active leiomyomas and few cellular leiomyomas, however that is still lesser as compared to leiomyosarcomas and even borderline neoplasms. Ki-67 expression in atypical leiomyomas was comparable to usual leiomyomas. Finally, usual leiomyomas showed minimum ki-67 expression of all these subcategories of uterine smooth muscle neoplams.

The criteria for establishing diagnosis of leiomyoma, borderline neoplasms (STUMP) and leiomyosarcomas has been constantly changing over the years from the initial and essential significance of the number of mitoses, nuclear atypia to the current significance of the presence of coagulation necrosis. No convention of the applied criteria proved to be completely safe and clear in establishing diagnosis.

In the past, many investigated presence and expression of various proliferative factors and hormone receptors in the cells of the smooth muscle neoplasms, which motivated us to contribute to the research of the expression of the proliferative factor Ki-67 by investigating our own material. We have chosen to measure expression of Ki-67 as a number of positive cells/100 cells count because it is acceptable and affordable in every day's practice.

We compared our data with previously presented studies. *Zhai et al.*[12] collaborates based their results of Ki-67 reactivity on the number of positive cells per 10 high power fields (HPF) of microscope and their results can not be compared with others. *Amada et al.*[15] didn't found reactivity of Ki-67 in LM, *Mayerhofer et al.*[13] found reactivity of Ki-67 in one tenth (2/25) of LM and *O'Neil et al.*[14] found Ki-67 reactivity in two fifths (4/10) of LM. We found ki-67 reactivity in (2/5) of our LM (<5%). *Mayerhofer et al.*[13] didn't found Ki-67 reactivity (0/22) in STUMP and *O'Neil et al.*[14] found Reactivity for Ki-67 in half (2/4) of STUMP. We found reactivity for Ki-67 in all (3/3) of STUMP (10-19%). *Amada et al.*[15] found 3.6% reactivity for Ki-67 in nine tenths (21/24) of LMS and 15% reactivity for Ki-67 in three fifths (14/24) of LMS, *Mayerhofer et al.*[13] found reactivity for Ki-67 in half (10/20) of LMS and *O'Neil et al.*[14] found reactivity for Ki-67 in four fifths (20/22) of LMS. All (2/2) of our LMS show reactivity for Ki-67 (>20%). In a case report, by *Suzana et al.*[16], they found atypical leiomyoma showing <10% ki-67 expression. In our case we found all (4/4) atypical leiomyomas, showed similar results. Not much literature has been published related to ki-67 expression in other variants of benign leiomyoma for comparision. Our study showed that majority (9/12) mitotically active leiomyomas showed relatively higher (10-15%) ki-67 expression with the rest (3/12 ) showed <10 %. All Cellular leiomyomas in our study showed ki-67 positivity with most of them (23/24) showing <5% expression, comparable to usual leiomyomas and only 1/24 showed relatively higher ( 5-10%) expression of ki-67.

The negative/ lowest level of ki-67 expression in usual leiomyomas very well correlates with the predictable biological behavior of these benign neoplasms. Lower level of expression in most of the cellular leiomyomas also correlates with the biological behavior of cellular leiomyomas, which are known to behave in a benign fashion comparable to usual leiomyomas. Only 1/24 cellular leiomyomas relatively higher

expression, though far lesser than borderline neoplasms and leiomysarcomas. However, this can alert histopathologist to recheck their diagnosis and also can be important for the clinician as these patients should be closely monitored for any unusual tumor progression in future. Mitotically active leiomyomas as their name implies express higher ki-67 positivity, indicating their high proliferation rate, which fits well with their histopathological diagnosis. On the other hand , in contrast to the alarming terminology given to atypical leiomyomas, the relatively lower level of ki-67 expression indicates that they belong to the benign category and are mere morphological variants of benign leiomyomas.This finding is very important as these are the most controversial neoplasms and cause greatest concern for the histopathologists and clinicians. Relatively higher level of ki-67 expression in borderline neoplasms (10-19%) mandates their close follow-up in the future, but helps in distinction from leiomyosarcomas which showed even greater (> 20%) ki-67 expression. Highest level of ki-67 expression by leiomyosarcomas clearly separates them from the benign neoplasms and also aids in their distinction from the borderline neoplasms.

## CONCLUSION

Major diagnostic features, as number of mitoses per 10 HPF, nuclear atypia, presence and extent of coagulation necrosis have limitations to predict biological behavior in uterine smooth muscle neoplasms. Though they are the basis for making diagnosis in these neoplasms, yet additional relevant parameters are needed, particularly in problematic cases. Immunostaining for Ki-67 expression in specific case eases diagnosis.

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