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Case Report

Uterine leiomyoma with bizarre nuclei – A series of four cases

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ABSTRACT

Uterine leiomyoma is the most common benign mesenchymal tumor of the uterus occurring in females of reproductive age group and are derived from smooth muscle. Degenerative changes are usual in leiomyoma. There is a wide spectrum of morphological patterns in leiomyomas, among them 90% of leiomyomas are the conventional type or usual type. Leiomyoma with bizarre nuclei is an unusual variant of uterine leiomyoma with presence of marked nuclear atypia and pleomorphism. However, there is low mitotic activity (< 5 mitoses/10 high power fields), absence of tumor cell necrosis and intermixed normal spindled smooth muscle cells. The present study describes histopathological analysis of 4 cases of leiomyoma with bizarre nuclei. All these cases underwent abdominal hysterectomy for leiomyomas in the uterus. The age range was 47 to 52 years. On gross examination the cases had well-defined masses with grey white, whorled areas and microscopic impression was leiomyoma with bizarre nuclei. These cases had low mitotic activity ranging from 1 to 3/ 10 high power fields and absence of tumor necrosis. Ki 67 index was 0.5 -1.0%. Leiomyoma with bizarre nuclei can create a diagnostic dilemma due to marked nuclear atypia, multinucleated tumor cells and karyorrhectic cells resembling mitotic figures. Hence it is important to rule out more aggressive and malignant mesenchymal tumors.

1. Introduction

Leiomyoma is the most common benign neoplasm of the uterus, occurring predominantly in the reproductive age group.[1,2] As per previous studies, the growth of leiomyoma depends up on estrogen and progesterone,[2] role of phosphorylation of proteins for the growth of leiomyoma was suggested by Ura et al.[3] A wide range of morphological variants and secondary changes are seen in leiomyoma.[1] Leiomyoma with bizarre nuclei (LBN) is an uncommon variant of leiomyoma.[2] This lesion was first reported in 1909 by Kelly and Cullen, they named it "sarcomatous degeneration" later some authors used terms such as "degenerative cytologic change," "symplastic cells," and "leiomyosarcoma in situ".[4] The terminology 'bizarre leiomyoma" was used by Christopherson et al in 1972.[2] In 1994, it was termed atypical leiomyoma and as per Bell's criteria it has moderate to marked nuclear atypia, mitosis <10/ high power fields (HPF) and no tumor cell necrosis.[5] Previous studies have used the following terminology such as atypical leiomyoma with low risk of recurrence, atypical leiomyoma, symplastic leiomyoma, and pleomorphic leiomyoma.[5,6] However, the latest 2020 World Health Organisation (WHO) classification discourages the above terms. As per 2020 WHO classification LBN is a subtype of leiomyoma with bizarre cells in a multifocal to diffuse distribution with a background of conventional leiomyoma.[2] The mitotic count in LBN is <5 mitoses/ 10 HPF of 0.55-mm diameter and 0.24-mm^2 area and LBN with 5–9 mitoses/10 HPF should be considered in the

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category of smooth muscle tumors of uncertain malignant potential (STUMP).[2]

2. Case Reports

The cases studied were females ranging from 47 year to 52 years of age. All these cases presented with abnormal uterine bleeding. The summary is described in (Table 1). Two of the cases were post-menopausal females. Duration of symptoms ranges from 6 months to 1 year. Pelvic ultrasonography (USG) revealed multiple intramural fibroids and single sub-serosal fibroid in one case each. Two patients had single sub-mucosal fibroid. Abdominal hysterectomy was done in all cases and sample was sent for histopathology. On gross examination, externally all cases showed bulky uterus. Cervix was unremarkable. On the cut section endometrial cavity was regular and fibroids had grey white and whorled appearance (Figure 1). The mean diameter of fibroids was 5 cm. The diameter ranged from 3.5 cm to 7 cm. Representative sections were taken and slides were stained by Hematoxylin and Eosin.

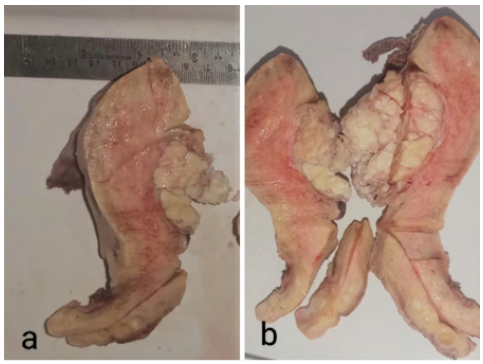

Figure 1: a,b : Cut sections of fibroids, submucosal fibroid with grey white cut surface and well-defined borders.

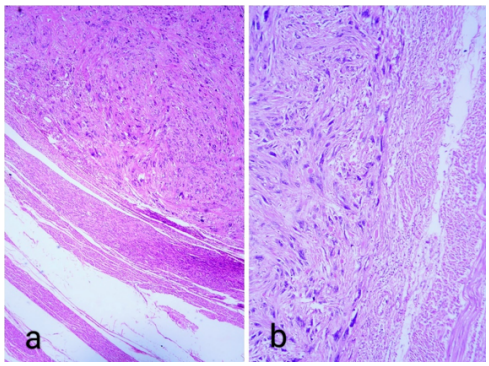

Figure 2: Leiomyoma with bizarre nuclei;**a:** Well circumscribed neoplasm (40x HE); **b:** There is no infiltration of tumor into surrounding smooth muscle (100x HE)

On microscopic examination, sections studied from endometrium showed glands and stroma in the proliferative

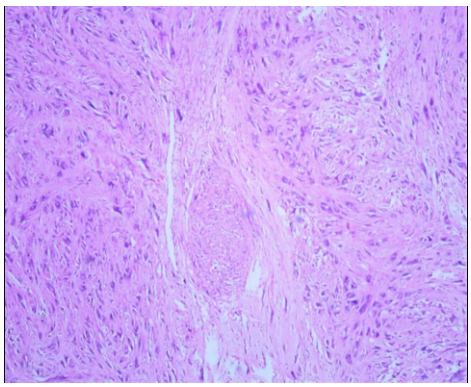

Figure 3: Nerve at the centre is not infiltrated by the tumor (100 HE).

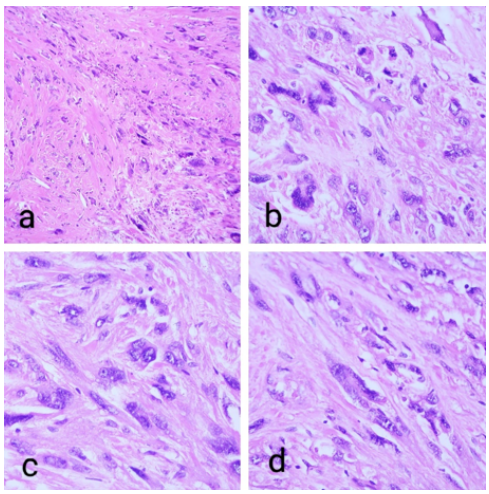

Figure 4: a: Tumor with hyaline stroma. (100x HE); **b,c,d:** The tumor cells with marked atypia, bizarre nuclei and tumor giant cells (400x HE)

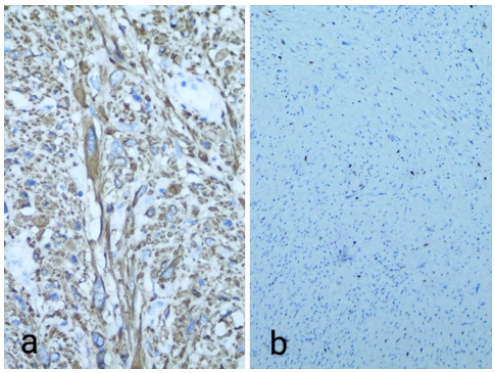

Figure 5: a: Tumor cells with cytoplasmic positivity for H - Caldesmon. (400x HE); **b:** The tumor cells with low Ki 67 index (400x HE)

Table 1: Summary of all four cases, abbreviation: NA: Not applicable.

Case and findings	Case 1	Case 2	Case 3	Case 4
Age	47	49	59	52
Abnormal uterine bleeding	Present	Present	Present	Present
Post menopausal bleeding	NA	NA	Present	Present
Multiple fibroids	Present	NA	NA	NA
Single fibroid	NA	Present	Present	Present
Location	Intramural	Sub-serosal	Sub-mucosal	Sub-mucosal
Degeneration	Hyaline	Absent	Absent	Hyaline
Mitosis (/10 HPF)	3	2	1	2
Atypical cells	Present	Present	Present	Present
Multinucleated cells	Present	Present	Absent	Present
Tumor necrosis	Absent	Absent	Absent	Absent
Infiltration	Absent	Absent	Absent	Absent
Ki 67 Index	1 %	0.7%	0.5%	1%
H- Caldesmon staining	Positive	Positive	Positive	Positive

phase in two cases and features of atrophy in two cases. Sections from cervix showed chronic cervicitis in all the cases. The myometrium showed presence of leiomyoma with bizarre nuclei. In all the cases, sections from the leiomyoma showed well circumscribed neoplasm with fascicles and bundles of smooth muscle with plump cigar shaped nuclei and abundant pink cytoplasm (Figures 2 and 3). Hyaline change was noted. Multiple foci of atypia were seen, these atypical cells had bizarre hyperchromatic nuclei and tumor giant cells were also seen (Figure 4). Mitotic activity ranged from 1/ 10 HPF to 3 / 10 HPF; atypical mitosis was not seen. There was no tumor cell necrosis in these cases. Neural involvement was not seen (Figure 3). Background had bland spindle cells. Immunohistochemistry revealed positive H- caldesmon in cytoplasm of tumor cells. The Ki 67 index ranged from 0.5% to 1% (Table 1 , Figure 5). The final diagnosis was given as leiomyoma with bizarre nuclei. On follow up all of these patients had no recurrence.

3. Discussion

Neoplasms arising from smooth muscle are the most common among all the uterine mesenchymal tumors.[1] Uterine leiomyomas usually occur in the reproductive age group.[1,2]The etiopathogenesis of leiomyoma is still not described in detail. Various different recurrent chromosomal abnormalities are associated with leiomyomas such as rearrangements of chromosomes 6 and 12. Mutations in the MED12 gene, which encodes a component of the RNA polymerase transcription complex, have been identified in up to 70% of leiomyomas. Growth of leiomyoma is stimulated by estrogens hence these tumors might shrink in post-menopausal females.[1] The three main uterine leiomyoma molecular subtypes include, tumors with MED12 point mutations, tumors with biallelic loss of FH, and tumors with HMGA2 overexpression; there are few reports of RAD51B::NUDT3 fusion in leiomyoma.[5,7]

There is a wide spectrum of histological variants of leiomyoma including cellular, leiomyoma with bizarre nuclei, mitotically active, Fumarate hydratase deficient (FHDL), hydropic, myxoid leiomyoma, apoplectic, epithelioid, lipoleiomyoma, leiomyoma with lymphoid infiltration and diffuse leiomyomatosis.[1,2,8] LBN was originally regarded as a tumor with a low risk of malignant behaviour, however studies have shown the benign nature of this lesion.[5]

All the cases in the present study were treated by simple hysterectomy. As per study by Gregova et al, there was recurrence rate of 42% after myomectomy, the mean age was 43 years in their study.[5] In a study by Kefeli et al the mean size of neoplasm was 6.1± 4.9 cm in diameter (range: 0.5– 25 cm) and tumor diameter was <5 cm in 50% of the patients.[4] In their study the most common location was intramural (37%).[4] In the present study 3 out 4 cases showed fibroids of size 5 cm diameter or less, mostly submucosal.

On histopathological examination, all four cases showed similar morphology. As per Guo et al the diagnostic criteria for LBN are focal, multifocal, or diffused bizarre cells on a background of typical leiomyoma cells and is characterized by moderate-to-marked nuclear atypia, low mitotic count (≤5 mitoses/10 HPFs) but with karyorrhectic nuclei, and no tumor cell necrosis.[2] In the present study these criteria were met by all the cases. In LBN the Nucleoli are usually small or absent, but occasional cases have eosinophilic giant nucleoli; such cases should be evaluated further.[2] The features which differentiate FHDL are alveolar-type edema, staghorn vessels, scattered bizarre nuclei, eosinophilic cytoplasmic (rhabdoid) inclusions, eosinophilic giant nucleoli with a peri-nucleolar halo, ovoid nuclei sometimes arranged in chains, and immunohistochemical (IHC) staining showing negative fumarate hydratase (FH) expression in tumor cells. Meticulous histopathological examination of nuclear

features and IHC is required for differentiating LBN from FHDL.[9] In a study by Tabrizi et al, the percentage of Ki67 was 0.85% in cases of LBN.[10] Sung et al have reported Ki 67 expression in less than 5% of atypical nuclei with one recurrent case.[11] In the present study the Ki 67 index ranged from 0.5% to 1%. PHH3 (Phosphohistone H3), is a mitosis-specific IHC marker and is more specific marker than Ki-67 (which marks nuclei in all active phases of cell cycle) to determine mitotic rate.[2] PHH3 expression is significantly increased in leiomyosarcoma (LMS) than in LBN, which is useful in the differential diagnosis of the two lesions. Other markers which are useful in differentiating LMS from LBN are cyclin-dependent kinase inhibitor 1A (p21), proliferating cell nuclear antigen (PCNA), epidermal growth factor receptor (EGFR), catechol-O-methyltransferase (COMT), major vault protein (MVP), and alpha-thalassemia/intellectual disability syndrome X-linked (ATRX) and RB.[2]

4. Conclusion

To summarize, LBN is a benign histologic variant of Leiomyoma. The recurrence rate is very low. However, as these tumors have marked nuclear atypia, the other morphologic criteria for aggressive and malignant counterparts, such as tumor cell necrosis and high mitotic rate should be excluded, and meticulous sampling is mandatory for accurate diagnosis. More retrospective studies with larger sample size are needed to improve the understanding of the nature of LBN. Regular close follow up of these patients is of paramount importance.

5. Conflict of Interest

None.

6. Source of Funding

None.

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