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**Original Article**

# Uterine Leiomyomas: Are the Blood Vessels Main Culprit?

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**Abstract**

**Objective:** Evaluate their histology; particularly in reference to their blood vessels and surrounding matrix to determine the role of vascular endothelial damage in pathogenesis of leiomyomas.
**Methodology:** 60 cases of leiomyomas were studied by two consultant histopathologists
**Place and duration of study:** Combined Military Hospital & AJK Medical College, from October 2013-December 2013
**Results:** All leiomyomas showed significant vascular changes. There was brisk angiogenesis, endothelial cell damage, exudation of plasma with organization and fibrosis.
Conclusion: The vascular changes suggested hormonal effects; particularly estrogen dominance; appropriate management of theses may retard the process of fibrosis and smooth muscle hyperplasia.
**Key words:** Leiomyoma, Fibroid, Angiogenesis, fibrosis, endothelial cell damage, extravasation of plasma.

## Introduction

The uterine leiomyomas are the commonest benign pelvic tumors in reproductive age females.[1, 2] The genetic predispositions, prenatal hormone exposure, various growth factors and xenoestrogens are considered important contributing factors. It's more common in nulliparous, obese women and those with polycystic ovarian syndrome. Slight preponderance with diabetes and hypertension and African ethnicity is also noted .[3] Estrogen and progesterone support mitoses in smooth muscle cells of uterus. Their actions may be mediated through various cytokines, growth factors, hormones and apoptotic factors. The complex and highly coordinated actions of progesterone, estrogen, and prolactin are dependent on signaling which in turn commands the appearance of the individual nuclear receptors. The estrogen advances growth through stimulating IGF-1, EGFR, TGF Beta-1, TGF-beta3 and PDGF, and helps endurance of smooth muscle cells of leiomyoma by retarding p53, favoring anti-apoptotic factor PCP4 and opposing PPAR gamma signaling. Progesterone stimulates TGF-beta1 and TGF-beta3, EGF, and BCL2 expression and decreases expression of TNF-alpha. Progesterone decreases growth by down regulating IGF-1.[4, 5, 6, 7] Expression of TGIF is augmented in leiomyoma as compared to cells of myometrium.[8]

The leiomyomas are monoclonal tumors of smooth muscle cells of the myometrium. They are quite vascular. These tumors show exuberant stroma rich in collagen, fibronectin, and proteoglycan.[9, 10] These are surrounded by a pseudocapsule [11] The leiomyomas vary in number and size. The large leiomyomas may obstruct the uterine cavity and distort the uterine shape. These may produce menorrhagia, and polymenorrea explaining severe anemia in some patients. In some patients they may be responsible for infertility, recurrent abortions and premature labor.[10] Many

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hysterectomies are carried out for uterine leiomyomas incurring added morbidity and expenses.[11] Some centers use uterine artery embolization or ligation. Obviously non surgical measures to prevent, control and eliminate are worth exploring. Various hormonal manipulations to retard the growth of leiomyomas and prevent the associated symptoms are in vogue.[12] Benign vascular tumors are being treated by beta-blockers and corticosteroids, so such medical treatment against proliferating vessels of leiomyoma may provide cheaper and more compliant therapy to treat leiomyomas. The detailed and specific morphological studies may identify areas of therapeutic targets. This study was therefore planned to see the morphological pattern of uterine leiomyomas with regard to its vasculature.

## Methodology

A cross sectional study of on 60 uterine leiomyomas was carried out at the pathology departments of combined military hospital Muzaffarabad and Azad Jammu & Kashmir Medical College Muzaffarabad over the period of 3 months from October – December 2013. No discrimination was made on the basis of age, parity or number of leiomyomas. The history of medication was not available.

The gross tumor size was noted. Microscopically vascular density, vessel wall damage, amount of extracellular matrix and degree of smooth muscle cell proliferation was recorded by light microscopy for each case. One well fixed and well stained section was taken per case. The observations were on Olympus microscope two histopathologists separately. Means of all the observations was calculated. Following Operational Definitions are utilized: Observations were based on X 100 magnification.

1. **Tumor size**
   a. Small: <2cm in diameter
   b. Large: >2cm in diameter
2. **Vessel density**
   a. Minimum: <50/10HPF
   b. Moderate: >50-<100/10HPF
   c. Marked: >100/10HPF
3. **Vessel wall damage**
   a. Minimal: Endothelial cell damage or thick basement membrane
   b. Moderate: Hemorrhage and edema in the vessel wall
   c. Marked: Vascular wall fibrosis and narrowing of lumen or sclerosis
4. **Extra cellular matrix/Collagen amount**
   a. Minimum: Interfascicular and perifascicular collagen
   b. Moderate: Large areas of collagen with myocyte vacuolation and shrinkage
   c. Marked: Extensive areas of collagen with loss of myocytes and vessels
5. **Smooth muscle proliferation**
   a. Minimum: 100 smooth muscle nuclei/HPF
   b. Moderate: 101-200 smooth muscle nuclei/HPF
   c. Marked: 200 smooth muscle nuclei/HPF

## Results

Total 60 uterine leiomyoma were studied. Frequency of size of tumor, vascular density, vessel wall damage and extracellular matrix among these cases is shown in table -1.

**Table 1. Vascular Pathology in leiomyomas.**

| Size of tumor | Vascular density | Vessel wall damage | Extracellular matrix/collagen | Smooth Muscle proliferation |
|---|---|---|---|---|
| <2cm- 13=21.6% | Minimum=13(21.6%) | Mild=5 (8.3%) | Minimum=7 (4.2%) | Marked=30 (50%) |
| >2cm47=78.3% | Moderate=32 (53.3%) | Moderate=36 (60%) | Moderate=43 (25.8%) | Moderate=20 (33.3%) |
| | Marked=15 (25%) | Marked=19 (11.4%) | Extensive=10 (30%) | Marked=10 (16.6%) |

The sections of the leiomyomas' vessels showed subtle endothelial cells smudging along with exudation of the plasma fluid within the vessel walls as well as in the surrounding stroma. (Figures 1&2)

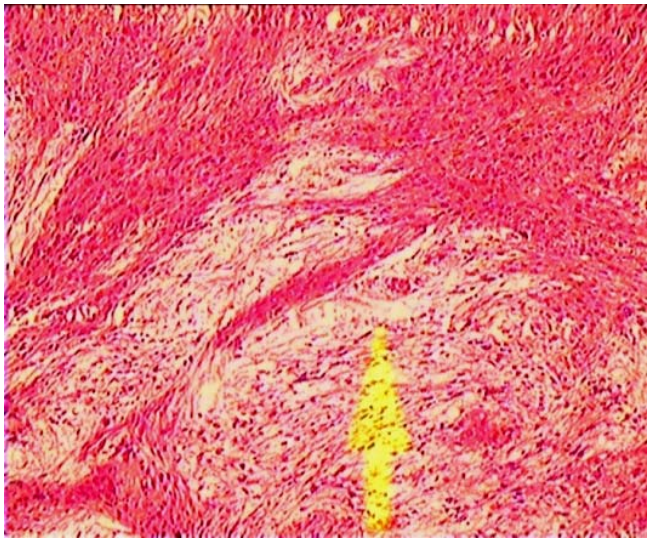

**Figure 1: Perivascular loose matrix containing many thin walled capillaries (H &E X 400)**

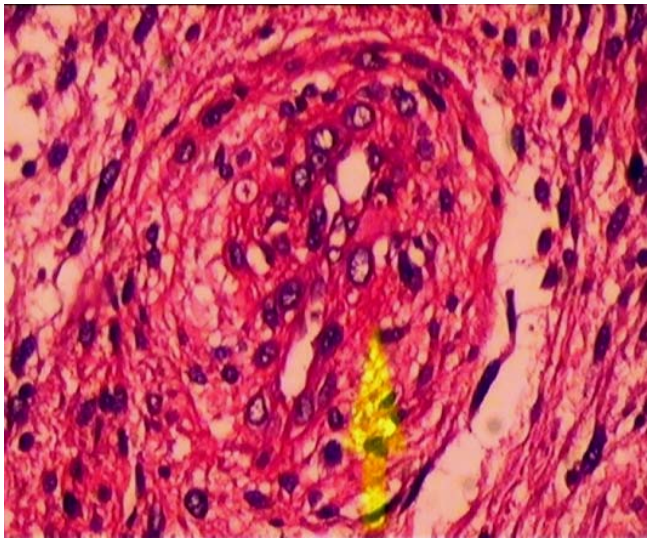

**Figure 2: Hemorrhage and edema within the vessel wall with reactive endothelial cells (H&E X 400)**

Brisk new capillaries are seen in the vicinity of the larger vessels in the surrounding loose matrix. At other places there is gradual replacement of the loose matrix with fibrosis. (Figures 3&4)

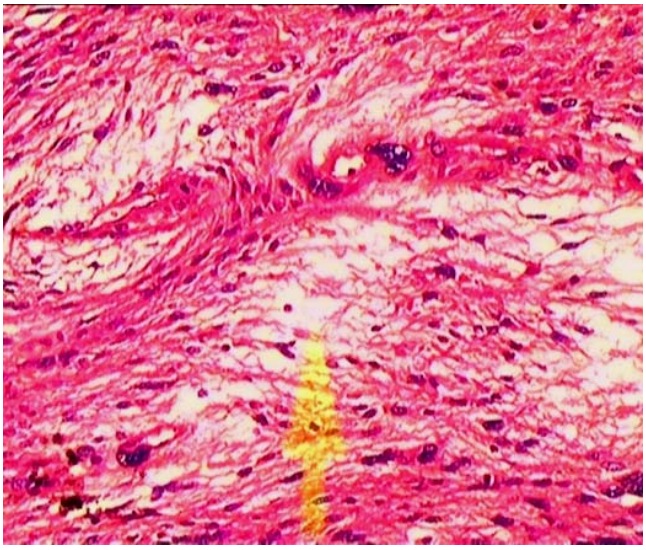

**Figure 3: Loose perivascular matrix with new vessels and some fibrosis. Note reactive large multilobed endothelial cell (H&E X 100)**

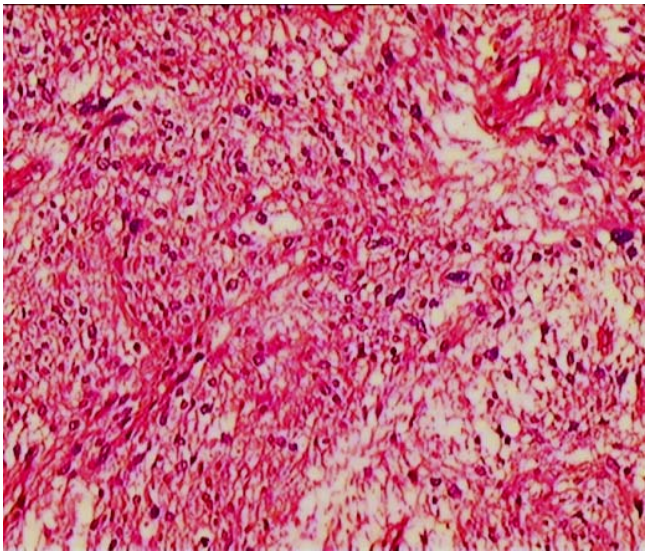

**Figure 4: Marked neovascularization in the loose matrix. Note smudgy vessels (H&E X 400)**

It seemed that exuded plasma due to endothelial damage may have provided a good milieu for the neovascularization and gradual fibrosis. (Figure 5) Smaller fibroids showed more vascular density and smooth muscle cell proliferation. While there was lesser vessel wall damage and extracellular matrix deposition as compared to larger fibroids. At times focal areas of infarcts are seen indicating the marked vascular compromise (figure 6).

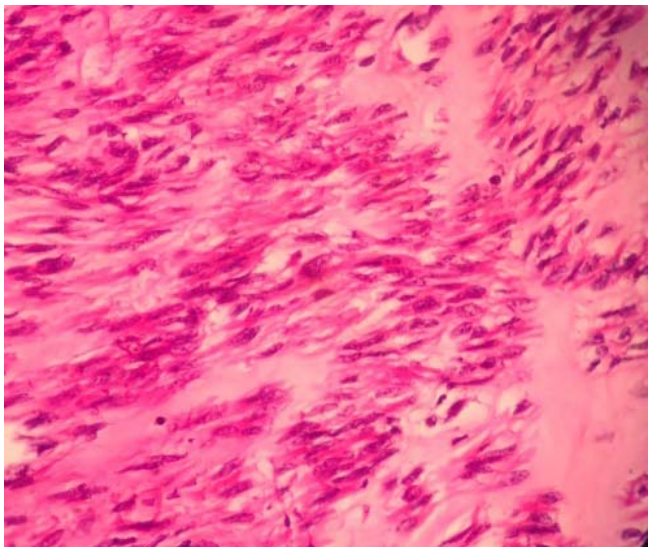

**Figure 5: Fascicles of proliferated smooth muscle cells with intervening areas of edema and fibrosis (H&EX 400)**

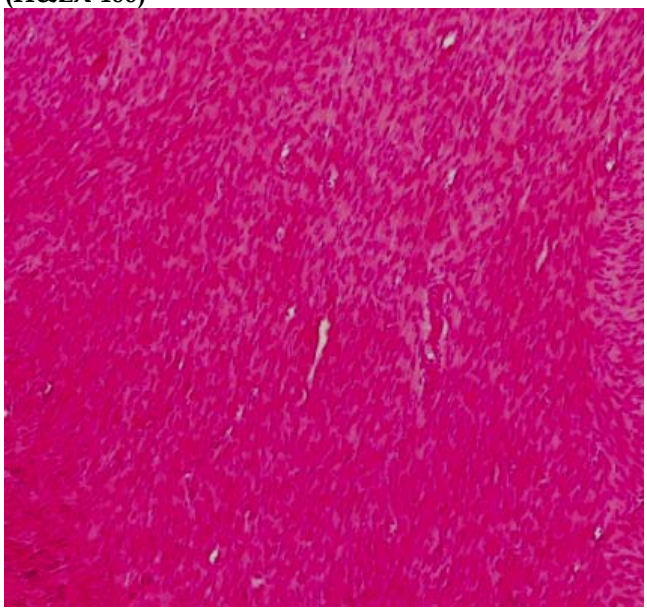

**Figure 6: Areas of ischemic necrosis in leiomyoma. The nuclei are pale and lost chromatin. (H&E X 100)**

Vascular and smooth muscle changes are shown in small leiomyomas in Figure 7 and in large leiomyomas in figure 8.

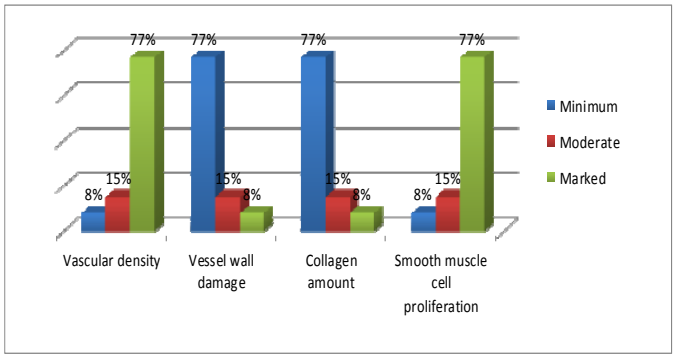


**Figure 7. Vascular and smooth muscle changes among smaller fibroids**

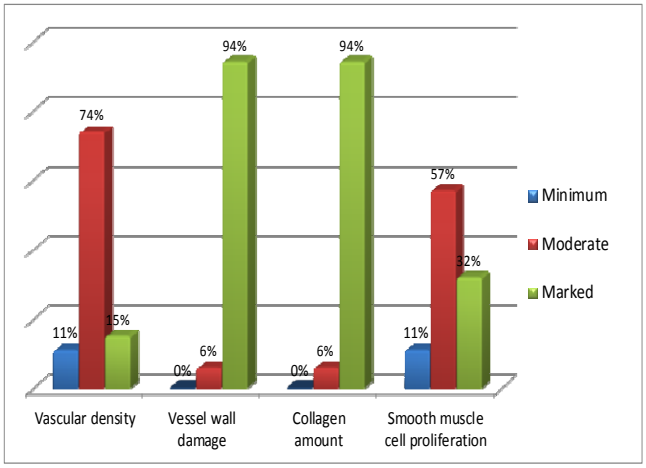


**Figure 8: Vascular and smooth muscle changes among larger fibroids**

## Discussion

Although uterine leiomyomas are the commonest benign tumor in women, their growth regulation is not clearly understood. It is believed that angiogenesis, may be the starting event.

Smaller leiomyoma in our study show marked vascular and smooth muscle cell proliferation. A study by Cheryl et al showed that vascular endothelial growth factor VEGF-A, a primary regulator of angiogenesis is upregulated in uterine leiomyomas and surrounding myometrium.[12] Vascular endothelial growth factor stimulates the growth of vessels and thus provides more nutrients and oxygen to proliferating cells of leiomyoma according to the study of Hyder SM et al. [13]

Larger fibroids in our study show vascular wall damage and smooth muscle atrophy along with fibrosis and edema. The above mentioned studies also support the role of angiogenesis and leakiness of newly formed vessels leading to increase in size and complications of leiomyoma.

## Conclusion

All uterine leiomyomas showed significant vascular changes; New and smaller leiomyomas displayed marked neovascularization and smooth muscle cells proliferation. As their size grows vessel wall damage is more apparent with lots of extracellular matrix deposition and fibrosis. These changes may be due to hormonal effects particularly relative estrogen excess or domination. Appropriate management of hormonal effects may prevent birth of leiomyomas or their progress!

**Limitations and strengths of study:** Uterine Leiomyomata have been rarely studied histologically for the vascular changes.

Sample size was small.

Vascular growth factors could not be studied simultaneously due to non-availability of Immunohistochemistry.

**Food For Thought:** Animal studies need to be done to find out if any medical therapy targeted against vascular proliferation can be applied to reduce the growth of smaller leiomyomas to larger ones and prevent formation of more leiomyomas in patients already having leiomyomas.

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