ORIGINAL ARTICLE

Uterine Leiomyomas: An ENIGMA

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ABSTRACT

Introduction: Leiomyomas are benign tumors composed of smooth muscle cells and varying amounts of fibrous connective tissue commonly encountered in women of reproductive age group. Leiomyomas need hormonal milieu for their growth and maintenance. Unopposed estrogenic stimulation manifests as leiomyomas undergoing secondary changes, endometrial proliferation or hyperplasia, and other associated pathological findings.
Objective: To study and analyze various histopathological changes within uterine leiomyomas in hysterectomy specimens. And also, to analyze the associated endometrial and adnexal structures pathology.
Materials and Methods: A 4 years retrospective study from June 2010 to June 2014 conducted in the Department of Pathology and Obstetrics and Gynecology, ESIC Medical College and PGIMSR, wherein 820 hysterectomy specimens clinically diagnosed as uterine leiomyomas were subjected to histopathological examination and relevant clinical data were analyzed.
Results: Leiomyomas occurred mostly in women aged 31-50 years (90.23%). Menorrhagia (49.36%) and pain abdomen (30.6%) were the chief clinical manifestations. Endometrial patterns commonly seen were proliferative and hyperplastic endometrium together accounting for 73.4% and dual pathology with adenomyosis was 29.1%. Four cases of tubercular etiology and a single case of granulosa cell tumor of ovary was noted.
Conclusion: Though hysterectomy is a routine procedure in the management of uterine leiomyomas, occasional cases of tumor or infective pathology may be missed. Therefore, histopathology is mandatory and conscientious quest must be done for confirmed diagnosis and ensuring optimal management.

Key Words: Endometrial changes, hysterectomy, leiomyomas

INTRODUCTION

Leiomyomas are benign tumors composed of smooth muscle cells and varying amounts of fibrous connective tissue. These synonymously termed as fibromyomas, fibroids, or myomas are the commonly encountered benign uterine neoplasms in women of reproductive age group accounting for 5-20%.[1-3] Complex interactions of sex steroid hormones and local growth hormones with mutations in the normal myometrium are being considered as the possible etiology. Leiomyomas need hormonal milieu for their growth and maintenance as evidenced by the molecular studies that they exhibit more estrogen receptors than normal myometrium.[3-5] Unopposed estrogenic stimulation manifests as leiomyomas undergoing secondary changes and endometrial proliferation or hyperplasia.[3-8] However, there are very few studies to elaborate on these pathological changes; hence, in this context the present study was taken up.

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Objective

1. To study and analyze various histopathological changes within uterine leiomyomas in hysterectomy specimens.
2. And also, the associated endometrial and adnexal structures pathology.

MATERIALS AND METHODS

The present study was conducted in the Department of Pathology, ESIC Medical College and PGIMSR and ESIC Model Hospital, Rajajinagar, Bengaluru, India, over a period of 4 years from June 2010 to June 2014. A total of 820 hysterectomy specimens with or without salpingo-oophorectomy diagnosed clinically and radiologically as uterine leiomyomas were subjected to examination. Brief demographic and clinical data of patients were collected.

On receipt of surgical specimen, they were fixed in 10% neutral buffered formalin for 24-48 h. A detailed gross examination of uterus and cervix with or without bilateral adnexa was carried out. Well circumscribed gray to tan lesions with whorled appearance was considered as leiomyoma and details related to its location, number, and secondary changes were noted. A minimum of two sections from cervix, endomyometrium, and one section each of fallopian tubes and ovaries were taken. Moreover, representative additional sections from leiomyomas and other abnormal areas were also taken, processed, and paraffin embedded. The blocks were sectioned and stained with hematoxylin and eosin. A detailed microscopic histopathological examination pertaining to endometrial glandular and stromal changes was noted. Myometrial and leiomyomatous histopathological changes in terms of secondary changes, variants, nuclear atypia, mitosis, and coagulative necrosis were studied. In addition, tubal and ovarian findings were collected to arrive at final diagnosis. Diagnosis of adenomyosis was considered when endometrial gland and stroma were noted within one low power field from endomyometrial junction. Specimens having more than one pathological change, all findings were cumulatively considered and included for further appropriate diagnosis.

Statistical analysis

The data were analyzed using Social Sciences software version 18.0 (SPSS Inc, Chicago). Obtained parameters were evaluated using descriptive statistical analysis and presented in terms of percentage.

RESULTS

Eight hundred and twenty uterine leiomyoma hysterectomy specimens with or without salpingo-oophorectomy were studied. Of which, 80.24% (658 cases) were abdominal hysterectomies with bilateral salpingo-oophorectomy specimens and remaining 19.76% (262 cases) were only hysterectomy specimens (abdominal and vaginal). In the present study, patients with leiomyomas were aged between second and fifth decades of life. The youngest was 26 years and oldest was 59 years of age. Majority 90.23% (740 cases) were in the age group of 31-50 years of life [Table 1]. Multiparous women 93.8% (769 cases) were commonly affected followed by primipara 4.6% and nulliparous women 1.6%. Menorrhagia was the most common clinical manifestation accounting to 49.36% (404 cases) followed by pain abdomen 30.6% (251) cases, dysmenorrhea 20% (164 cases), and a single patient complained of urinary retention. Diagnosis of uterine leiomyomas was made exclusively on clinical examination in 54.1% (444) cases. In the remaining 45.9% (376) cases, both clinical and ultrasonography (USG) findings were needed for diagnosis. However, USG was done on all the cases, and diagnosis on clinical findings was confirmed.

Most of the uteri showed unitary leiomyomas accounting for 70.9% (582) cases in the remaining 29.1% (238) cases, the number varied from 2 to 10. In the present study, with respect to the location, majority 48.9% (401) cases were intramural leiomyomas followed by subserosal 15.3% (125) cases, submucosal 2.9% (24) cases, and 32.9% (270) cases had leiomyomas in more than one location.

Grossly, 13.17% (108) cases of leiomyomas showed secondary changes [Figure 1]. Microscopically, various histopathological changes occurring within leiomyomas were present in 32.81% (269) cases [Table 2 and Figure 2]. Hyalinization in 19.51% (160) cases was the most common secondary degenerative change. Among the variants of leiomyomas, a single case of lipoleiomyoma, cellular leiomyoma, four cases (0.48%) of smooth muscle tumor of uncertain malignant potential (STUMP), and a single case of malignant transformation into leiomyosarcoma (LMS) were noted [Figure 3].

Microscopic examination of endometrium revealed 50.7% (416) cases of proliferative phase and 22.7% (186) cases of endometrial hyperplasia. Endometrial stromal changes noted were hemorrhage, chronic endometritis, and tubercular endometritis [Tables 3 and 4]. Dual

Table 1: Age-wise distribution of patients with leiomyoma

Age in years	Number	Percentage
20-30	37	4.52
31-40	338	41.21
41-50	402	49.02
51-60	43	5.25
Total	820	100

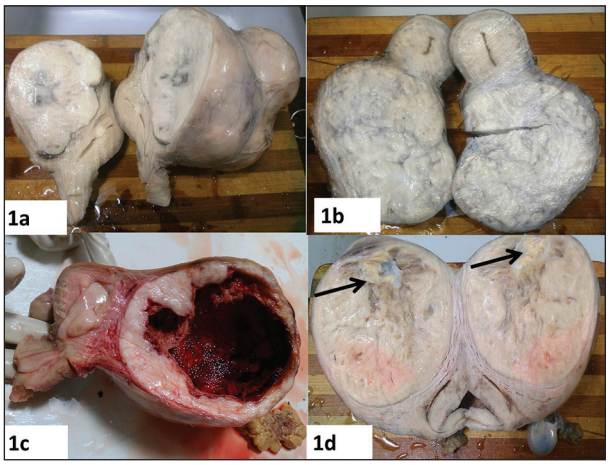

Figure 1: Gross morphology of hysterectomy specimen showing external bosselated surface and cut surface revealing leiomyoma with secondary change. (b) Cut surface showing cervical leiomyoma. (c) Cut surface showing uterine leiomyoma with cystic change and endometrial polyp. (d) Cut surface showing uterine leiomyoma with secondary change and lipomatous area

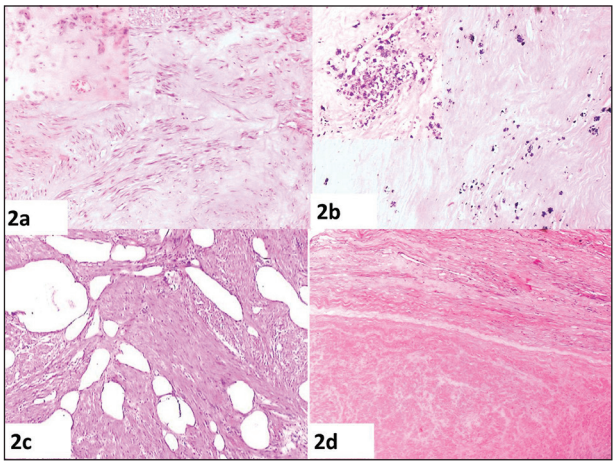

Figure 2: (a) H and E histopathology section showing leiomyoma with hyalinization. (b) Calcification (c) Cystic change (d) Red degeneration

pathology of leiomyoma and adenomyosis was noted in 29.1% (238 cases).

Other coincidental pathologies with uterine leiomyomas are depicted in Table 5 [Figure 4].

DISCUSSION

Leiomyomas are benign uterine neoplasm for which the most common gynecological procedure performed is hysterectomy. Charles Clay was the first to perform subtotal and total hysterectomy in Manchester, England, in 1843 and 1929, respectively.[9,10] Benign conditions such as leiomyoma, dysfunctional uterine bleeding, adenomyosis, pelvis inflammatory diseases, endometriosis, pelvic organ prolapse account for major hysterectomies, and rest for malignancy.[11,12] Of these benign lesions, leiomyoma followed by adenomyosis is the most common indication for hysterectomy.[13] It is a successful procedure done in terms of symptom relief; patient satisfaction; and definitive cure in many diseases.[11-13]

Leiomyomas are commonly seen in women of reproductive age.[1-3,7] The present study had greater frequency between 31 and 50 years (90.23%) of age group similar to studies by Ashraf,[14] and Begum and Khan[7] whereas in contrast, Hafiz *et al.*[15] observed that affected females were a decade lesser than 20-40 years of age possibly since they included only menorrhagic patients with fibroid. Multiparous women (93.8%) were found to have leiomyomas more frequently than nulliparous (1.6%) analogous to a study by Begum and Khan,[7] in contrast to a study by Derek[16] who observed fibroids are more common in nulliparous or infertile patients since he included more of asymptomatic infertile patients with fibroids.

Table 2: Histopathological within leiomyomas

Secondary changes and variants	Number	Percentage
Hyalinization	160	19.51
Cystic change	41	5
Myxoid change	33	4.03
Hemorrhage	18	2.2
Calcification	08	0.98
Red degeneration	02	0.25
Lipomatous	01	0.12
Cellular leiomyoma	01	0.12
Stump	04	0.48
Malignant-leiomyosarcoma	01	0.12
Absent	551	67.19
Total	820	100

Table 3: Endometrial changes with uterine leiomyomas

Endometrial changes	Number	Percentage
Proliferative phase	416	50.7
Simple hyperplasia	186	22.7
Secretory phase	144	17.57
Senile cystic atrophy	23	2.8
Atrophic endometrium	31	3.79
Proliferative with adenomyomatous polyp	20	2.44
Total	820	100

Table 4: Endometrial stromal changes in association with uterine leiomyomas

Endometrial stromal changes	Number	Percentage
Hemorrhage	11	1.3
Chronic endometritis	07	0.85
Tubercular endometritis	02	0.24
Absent	800	97.56
Total	820	100

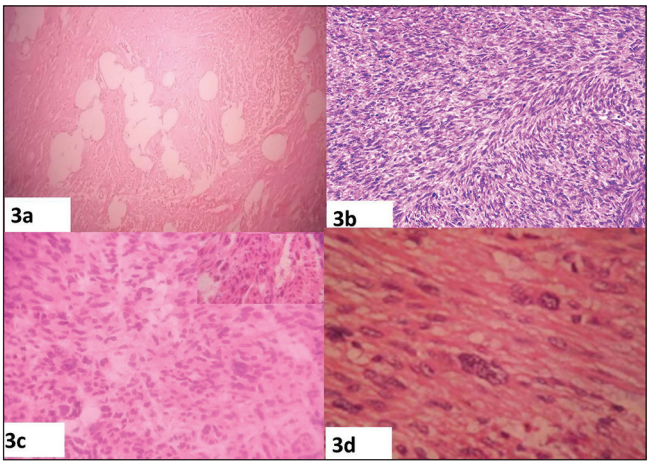

Figure 3: (a) H and E histopathology section showing leiomyoma with lipomatous change (b) Cellular leiomyoma (c) Smooth muscle tumor of uncertain malignant potential (d) Leiomyosarcoma

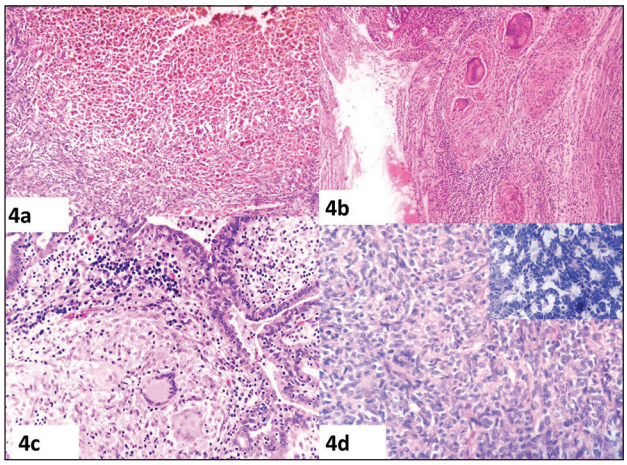

Figure 4: (a) H and E histopathology section showing chocolate cyst ovary (b) Tubercular endometritis (c) Tubercular salpingitis (d) Granulosa cell tumor of ovary

Table 5: Other pathologies associated with uterine leiomyomas

Other pathologies	Number	Percentage
Cervical fibroid	68	8.29
Broad ligament fibroid	13	1.58
Mucinous cystadenoma of ovary	34	4.14
Serous cystadenoma of ovary	49	5.99
Chocolate cyst of ovary	30	3.65
Granulomatous salpingitis	06	0.74
Tubercular salpingitis	04	0.49
Dermoid/mature cystic teratoma	04	0.49
Granulosa cell tumor of ovary	01	0.13
Absent	611	74.6
Total	820	100

Literature search shows patients with uterine leiomyomas are asymptomatic, but if symptomatic, the most common clinical manifestation noted is menorrhagia due to increased vascularity, increased endometrial surface, and altered uterine contractility.[7,17] In the present study also, menorrhagia was the most common clinical manifestation accounting to 49.36% followed by pain abdomen 30.6%, which may be due to degenerative changes in leiomyomas similar to a study by Begum and Khan,[7] and Jaiswal.[17] 54.1% of patients were diagnosed with uterine leiomyomas on clinical examination alone whereas USG was needed as additional factor (45.9%), similar to a study by Begum and Khan[7] and author concluded that USG is confirmatory with 80% accuracy. Abraham in his study stated that diagnosis of leiomyomas is usually done on clinical findings, but USG is helpful in ruling out that these tumors are not extrauterine masses or they have an extrauterine extension.[18] In the present study, number of leiomyomas in uterus varied from 1 to 10, of which 70.9% of patients had unitary leiomyomas in concordance with Rosario,[19] in contrast, study by Begum and Khan[6] had majority of multiples. Most of the leiomyomas were intramural in location (48.9%), similar to a study by Chhabra and Ohri[20] and Begum and Khan,[7] and Rosario.[19]

In the present study, secondary degenerative changes were noted grossly in 13.17% of cases. 32.81% of cases showed various histopathological changes microscopically. The degenerative changes in leiomyomas occur due to inadequate blood supply which may result in hyalinization, most common followed by cystic, hemorrhage, hydropic, or calcification, and very rarely malignant degeneration or LMS. The type of secondary change depends on the rapidity and degree of vascular insufficiency.[7,21,22] In the present study also, hyalinization was the most common secondary change similar to the study by Begum and Khan,[7] and Persaud and Arjoon.[21] Red degeneration occurs predominantly during pregnancy,[21,22] two of our cases were diagnosed during pregnancy and hysterectomy was performed after elective cesarean section. In addition, these secondary changes usually occur in old mature lesions and hence careful conscientious histopathological sampling should be carried out.[21,22]

Lipoleiomyoma is a rarer variant of uterine leiomyoma showing histological features of varying amounts of mature adipocytic cells amidst smooth muscle cells. Their incidence ranges from 0.03 to 0.2%.[23,24] This is similar to the incidence in our study accounting to 0.05%. In contrast, a study by Abraham and Saldanha had a higher frequency of 0.7%.[25]

Cellular leiomyomas are defined by the World Health Organization (WHO) as leiomyomas having significantly high cellularity compared to surrounding myometrium. They lack tumor necrosis, atypia, and mitotic figures.[3,25] Their incidence is usually <5%, in the present study, we encounter 0.12% of this entity.[3,25]

STUMP is defined by the WHO as smooth muscle tumor that cannot be histologically diagnosed as unequivocally benign or malignant. Microscopy reveals minimal atypical smooth muscle neoplasm with low mitotic index <10/10 high power field (hpf), but uncertainty about coagulative tumor cell necrosis.[2,3,26] In a study done by Ip *et al.*, 16 cases of STUMP were analyzed over a period of 14 years from eleven hospitals and concluded saying these are usually benign, but should be considered tumors of low malignant potential since they recur after years of hysterectomy. In their study, 2/16 cases showed recurrence after 80.8 months. Hence, these patients with STUMP need long-term surveillance.[26] In the present study, four cases were encountered over a period of 3 years; however, no one presented with any recurrence till date.

LMS malignant counterpart of leiomyoma accounts to 1-2% of uterine malignancies seen in the age group of 40-69 years.[2,3,27] These can arise in a preexisting leiomyomas or independently from myometrium. Microscopy shows hypercellular spindle cells with severe pleomorphism, nuclear atypia, more than 10/10 hpf mitotic figures, and coagulative tumor cell necrosis. LMS is a very aggressive tumor having high risk of recurrence and death, regardless of stage of presentation.[2,3,27] In the present study, a single case of LMS in association with leiomyoma was noted.

In the present study, the most common endometrial changes in association with uterine leiomyomas were proliferative phase and simple hyperplastic endometrium together accounted for 73.4% possibly due to hyper-estrogenic status in accordance with the study by Rosario,[19] Purandare and Jhalam,[28] Sanyal *et al.*,[29] and Chethana *et al.*[30] In the present study, atrophic endometrium was 3.79% similar to studies by Deligdish and Loewenthal *et al.*,[31] Chethana *et al.*,[30] and Rosario[19] and described these endometrial changes of normal, hyperplasia, and atrophy may be possibly due to irregular secretion of estrogens and mechanical effects of fibroid on endometrium. Simple hyperplasia is the most common accounting to 22.7% similar to a study by Teleman and Mihailovici,[32] wherein he adds leiomyomas have a protective role in capturing estrogen as a target tissue and hence progression to higher grades such as complex, atypical, or endometrial carcinomas is rarer.

Dual pathology of adenomyosis and leiomyomas was noted in 29.1% of patients in the present study similar to studies by Deligdish and Loewenthal,[31] Rizvi *et al.*,[33] and Rani and Thomas.[13] Coexistence of these lesions is also due to unopposed estrogen and entrapment of glands within hypertrophied myometrium. Diagnosis of adenomyosis remains an incidental histopathological finding in uterine tissues examined for other clinically suspected pathology.

Extensive literature search showed no studies who reported on the various associated pathologies in collision with uterine leiomyomas. In the present study, though the causative factor for hysterectomy was leiomyoma, there were varied incidental concurrent preoperatively undiagnosed lesions such as granulosa cell tumor of ovary (3.65%), dermoid cyst (0.49%), mucinous (4.14%), serous cystadenoma of ovary (5.99%), chocolate cyst of ovary (0.8%), and infective lesions such as tubercular endometritis and salpingitis. Two of our cases, middle-aged women diagnosed with uterine leiomyoma clinically when subjected to holoprosencephaly (HPE), there was incidental caseating granulomas involving whole of endometrium, myometrium, and fallopian tubes similar to a case report by Takkar *et al.*,[34] and he concluded to always look for additional pathology associated which may need further therapy. The granulosa cell tumor (GCT) of the ovary is classified as a sex-cord stromal tumor accounting to 1-2% of all ovarian tumors occurring in peri-and postmenopausal women. In the present study, a 40-year-old women diagnosed clinically with dysfunctional uterine bleeding and leiomyoma when subjected to HPE revealed a coincidental ovarian GCT, simple hyperplastic endometrium, and intramural leiomyoma similar to a case report by Kurioka *et al.*[35] Hence, the authors emphasize on imperative submission of all hysterectomy specimens for histopathology, thorough sampling, and diligent quest for associated pathologies in routine hysterectomy specimens, few of which may need further management and surveillance for the patient's well-being.

CONCLUSION

Leiomyomas are the most common benign smooth muscle tumors encountered frequently in multiparous women between third and fourth decades of life. The present study highlights the various gamut of infective and tumorous lesions seen in and around uterine leiomyomas of hysterectomy specimens which could be missed. Therefore, conscientious histopathological examination should be mandatory and of paramount importance for confirmed diagnosis, optimal management, and surveillance of the concerned patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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