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Histopathological Analysis Of Endometrial Changes In Association With Myometrial Lesions Of Hysterectomy Specimens

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Abstract

Background: The uterus is prone to develop several non-neoplastic and neoplastic conditions during the lifetime of a woman. The uterus consists of endometrium and myometrium which is under the influence of different hormones periodically. Many studies have shown many different types of lesions in the ovaries and fallopian tubes. The cervix is prone to many non-neoplastic and neoplastic conditions which are mostly seen in the reproductive age group. All these diseases are seen across all age groups and contribute significantly to increased morbidity and mortality among women.

Aim Of The Study: To assess the age distribution of the myometrial lesions in patients subjected to hysterectomy. To assess the endometrial changes in the types and sites of myometrial lesions in hysterectomy specimens. To analyze the histopathological changes of endometrium in association with myometrial lesions of hysterectomy specimens concerning age, LMP.

Methods This was a prospective and retrospective study performed on hysterectomy specimens received at the Department of Pathology, Chennai Medical College Hospital, and Research Centre for a period of one and half years from November 2016 to June 2018 after getting ethical clearance. A total of 250 cases in all age groups were included in the study. The endometrial patterns were analyzed in hysterectomy specimens with myometrial lesions. A total of 250 hysterectomy specimens with myometrial lesions are taken. A detailed gross examination was performed concerning the location and size of the leiomyoma, and the status of the endometrium and endometrial polyp if any were noted. Tissue bits from representative areas of the leiomyoma and endometrium were taken for histopathological examination and processed and paraffin blocks were made. Sections were cut at 5-micron thickness and stained with hematoxylin and eosin. Microscopic sections were studied and the following histologic features were recorded:

Results: Out of 250 patients, 68% (170) patients were from the age group 40 to 49 years. It was followed by patients from 30 - 39 years, 16% (40), and 50 - 59 years, 13.2% (33). The least number of patients were from the age group 60 - 69 years, 2.8%. Most leiomyomas were located intramurally 52.8% (132). It was followed by submucous 14.4% and intramural and submucous combination 10% location. The number of cases with subserous and a combination of intramucosal and subserous was 9.2% (23) and 8% (20) respectively. The least

number of cases were located in the submucous and subserous combinations [2.4% (6)] and intramural, subserous, and submucous combinations. The percent of cases associated with the proliferative phase and late secretory phases was 20.8% (52) and 16% (40) respectively. The percent of cases associated with simple hyperplasia, disordered proliferative phase, and atrophic endometrium was 11.2% (28), 10.8% (27), and 9.6% (24) respectively. Only 2.8% (7) were associated with LMP of less than seven days. Leiomyomas associated with post-menopause were 12.8% (32)

Conclusion: In this study, most of the myometrial lesions(leiomyoma) were seen in the 4th and 5th decades of life. Intramural location was seen more than other locations. The endometrial changes seen were hyperplasia(simple as well as complex) and infrequently carcinomatous change. The older group of women in this study had atrophic endometrium and relative changes. Many of the cases had persistent hyperestrogenic stimulus. Adenomyosis and my hyperplasia were frequent associations.

Keywords: Hysterectomy, Histopathology, Leiomyoma, Uterine prolapse, Menorrhagia

Introduction

Uterus is a vital reproductive organ subjected to many benign and malignant lesions which commonly result from various hormonal imbalances. The myometrium of the uterus is composed of bundles of smooth muscle that form the wall of the uterus. [1]The inner cavity of the uterus is lined by the endometrium composed of glands embedded in a cellular stroma. The endometrium is a dynamic tissue that undergoes physiologic and characteristic morphologic changes during the menstrual cycle as a result of the effect of sex steroid hormones like estrogen and progesterone produced in the ovary. [2]A myriad array of compounds has been identified in the endometrium including enzymes, hormones, and bioactive peptides. Normal values for endometrial thickness range from 2 to 16 millimeters, depending on the stage of the menstrual cycle.[3] The cycle begins with the shedding of the upper half to two-thirds of the endometrium, referred to as the functional, during menses. Under the influence of estrogen, produced by the granulosa cells of the developing follicle in the ovary, the remaining third (basalis) undergoes extremely rapid growth of both glands and stroma.[4]

Adenomyosis consists of both epithelial and stromal elements and is located about 2 to 2.5mm below the endometrial junction. Furthermore, leiomyomas are frequently associated with adenomyosis hindering the differential diagnosis. Adenomyosis has been difficult to diagnose without the surgical pathology of a hysterectomy specimen.[5] Uterine leiomyomas account for more than 75% of benign tumors in women of the reproductive age group. Studies have suggested that numerous hormones, growth factors, cytokines, and other signal transduction pathways have a role in the pathogenesis of leiomyoma. Estrogen and estrogen-related genes might play a predominant role in the growth rate of leiomyomas. [6]The normal myometrium of uteri expresses higher levels of estrogen receptors which is related to pathogenesis. The leiomyoma is composed of smooth muscle and fibrous tissue and is benign. Based on their location within the uterine wall, leiomyomas are classified into submucosal or sub endometrial, intramural or myometrial, and subserosal leiomyomas. The latter may be pedunculated and simulate adnexal masses.[7] Most of the leiomyomas undergo secondary changes in approximately 65% of cases. These include hyaline degeneration (63%), myxoid changes (19%), calcification (8%), cystic changes(4%), and fatty metamorphosis (3%). The leiomyosarcoma is the malignant counterpart of the leiomyoma and is the most common pure sarcoma of the uterus. [8] Hence this study attempted to study the histopathological changes in the endometrium with associated myometrial lesions in hysterectomy specimens.

Methods This was a prospective and retrospective study performed on hysterectomy specimens received at the Department of Pathology, Chennai Medical College Hospital, and Research Centre for a period of one and half years from November 2016 to June 2018 after getting ethical clearance. A total of 250 cases in all age groups were included in the study. The endometrial patterns were analyzed in hysterectomy

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specimens with myometrial lesions. A total of 250 hysterectomy specimens with myometrial lesions are taken. A detailed gross examination was performed concerning the location and size of the leiomyoma, and the status of the endometrium and endometrial polyp if any were noted. Tissue bits from representative areas of the leiomyoma and endometrium were taken for histopathological examination and processed and paraffin blocks were made. Sections were cut at 5-micron thickness and stained with hematoxylin and eosin. Microscopic sections were studied and the following histologic features were recorded: **Inclusion Criteria:** Patients undergoing hysterectomy for myometrial lesions presenting with clinical symptoms. **Exclusion Criteria:** Specimens of endometrial curettage and aspiration.Patients for whom hysterectomy is performed for non-myometrial lesions. A detailed gross examination was performed concerning the location and size of the leiomyoma, and the status of the endometrium and endometrial polyp if any were noted. Tissue bits from representative areas of the leiomyoma and endometrium were taken for histopathological examination and processed and paraffin blocks were made. Sections were cut at 5-micron thickness and stained with hematoxylin and eosin. Microscopic sections were studied and the following histologic features were recorded: Endometrial parameters - endometrium, phase, the appearance of glands, and stromal changes. Myometrial parameters- presence or absence of adenomyosis, type or variant of leiomyoma.

Stastical Analysis: Using This software, range, frequencies, percentages, means, standard deviations, chi-square, and 'p' values were calculated. Kruskal Walli's chi-square test was used to test the significance of the difference between quantitative variables and Yate's test for qualitative variables. A 'p-value less than 0.05 is taken to denote a significant relationship.

Results

Table 1 - Age Wise Distribution Of Patients

Age in years	No. of cases	Percent
30-39	40	16.0
40-49	170	68.0
50-59	33	13.2
60-69	7	2.8
TOTAL	**250**	**100**

Table :1 Out of 250 patients, 68% (170) patients were from the age group 40 to 49 years. It was followed by patients from 30 - 39 years, 16% (40), and 50 - 59 years, 13.2% (33). The least number of patients were from the age group 60 - 69 years, 2.8% (7).

Table 2 Distribution Of Endometrial Changes According To Age Group

ENDOMETRIAL CHANGES	AGE RANGE IN YEARS							
	30 - 39		40 - 49		50 - 59		60 – 69	
	F	P	F	P	F	P	F	P
PP	10	25.0	39	22.9	3	9.1		
ES	16	40.0	51	30.0	8	24.2		

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LS	5	12.5	33	19.4	2	6.1		
DPP	3	7.5	22	12.9	2	6.1		
SH	6	15.0	18	10.6	4	12.1		
CH			1	.6				
Atrophic			5	2.9	13	39.4	6	85.7
EIN			1	.6				
EC					1	3.0		
Others							1	14.3
TOTAL	**40**	**100.0**	**170**	**100.0**	**33**	**100.0**	**7**	**100.0**

Table 3:Distribution Of Leiomyoma Based On Location

S.No.	Location	Frequency	Percent
1	Intra mural	132	52.8
2	Sub mucous	36	14.4
3	Sub serous	23	9.2
4	Intra-mural and Sub mucous	25	10.0
5	Intramural and Subserous	20	8.0
6	Submucous and Sub serous	6	2.4
7	Intramural, Submucous, and Subserous	8	3.2
TOTAL		**250**	**100.0**

Table :3 Most leiomyomas were located intramurally at 52.8% (132). It was followed by submucous [14.4% (36)] and intramural and submucous combination [10% (25)] locations. The number of cases with subserous and a combination of intramucosal and subserous was 9.2% (23) and 8% (20) respectively. The least number of cases were located in submucous and subserous combinations [2.4% (6)] and intramural, subserous, and submucous combinations [3, 2% (8)]

Table 4 - DISTRIBUTION OF ENDOMETRIAL CHANGES IN LEIOMYOMA

S.No.	Endometrial Change	Frequency	Percent
1	Proliferative Phase	52	20.8

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2	Early Secretory Phase	75	30
3	Late Secretory Phase	40	16
4	Disordered proliferative phase	27	10.8
5	Simple Hyperplasia	28	11.2
6	Complex Hyperplasia	1	0.4
7	Atrophic Endometrium	24	9.6
8	Endometrial intraepithelial neoplasia	1	0.4
9	Endometrial carcinoma	1	0.4
10	Others	1	0.4
	TOTAL	**250**	**100.0**

Table 4 Thirty percent (75) of the cases reported were associated with the early secretory phase. The percent of cases associated with the proliferative phase and late secretory phases was 20.8% (52) and 16% (40) respectively. The percent of cases associated with simple hyperplasia, disordered proliferative phase, and atrophic endometrium was 11.2% (28), 10.8% (27), and 9.6% (24) respectively. There was one (0.4%, total 2%) case of each - complex hyperplasia, Endometrial intraepithelial invasion, endometrial carcinoma, and other.

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Graph 1 – Distribution Of Endometrial Changes According To The Site Of Leiomyoma

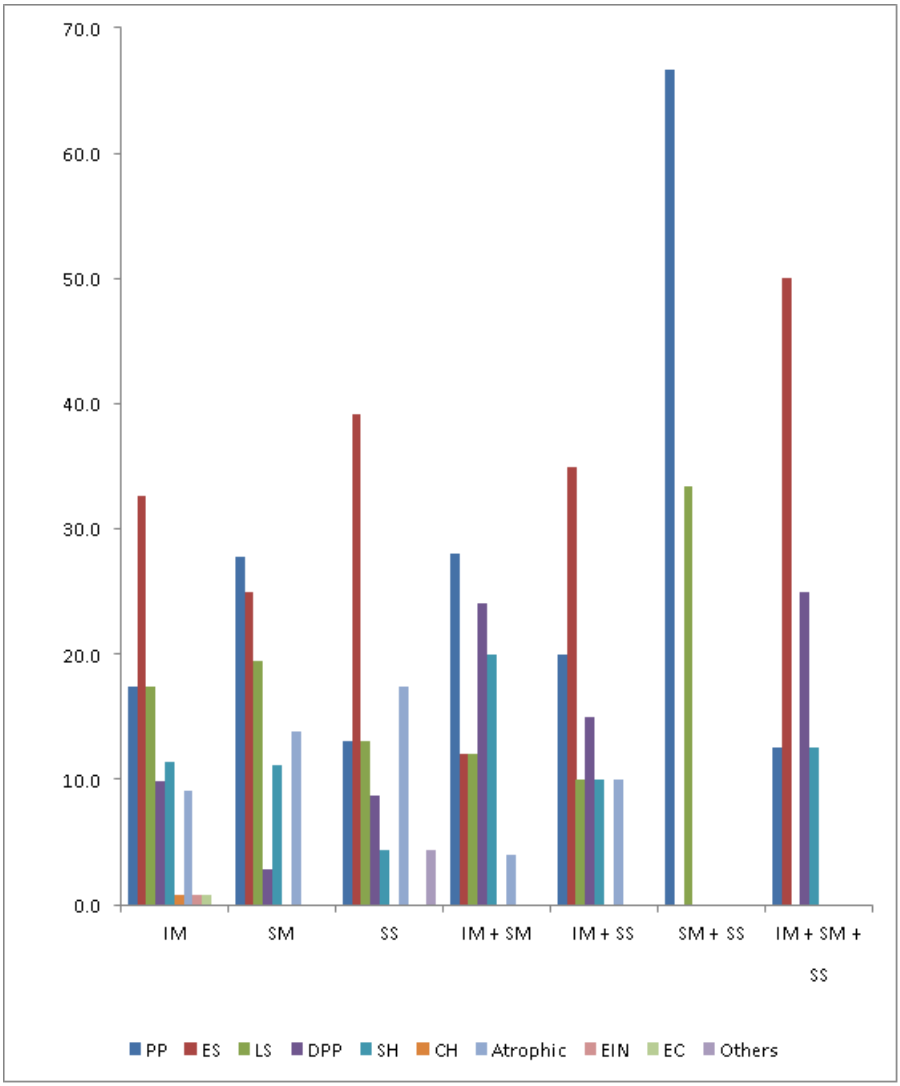

Table 5 - Distribution Of Leiomyoma According To Lmp

LMP in days	Frequency	Percent
< 7 days	7	2.8
7 to 15 days	55	22.0
16 to 30 days	97	38.8
> 30 days	59	23.6
Post-menopausal	32	12.8
TOTAL	**250**	**100.0**

Table 5 Majority of the leiomyoma cases 38.8% (97) had LMP of 16 to 30 days. It was followed by LMP of greater than 30 days [23.6% (59)] and 7 to 15 days [22% (55)]. Only 2.8% (7) were associated with LMP of less than seven days. Leiomyomas associated with post-menopause were 12.8% (32)

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Table 6 – Distribution Of Endometrial Changes According To LMP

ENDOMETRIAL CHANGES	LMP IN DAYS									
	<7		7 - 15		16 - 30		>30		Post-menopausal	
	F	P	F	P	F	P	F	P	F	P
PP	2	28.6	20	36.4	17	17.5	7	11.9	6	18.8
ES	3	42.9	19	34.5	41	42.3	11	18.6	1	3.1
LS			2	3.6	12	12.4	26	44.1		
DPP	1	14.3	6	10.9	13	13.4	6	10.2	1	3.1
SH	1	14.3	7	12.7	10	10.3	8	13.6	2	6.3
CH							1	1.7		
Atrophic			1	1.8	3	3.1			20	62.5
EIN					1	1.0				
EC					97	100.0			1	3.1
Others									1	3.1
TOTAL	**7**	**100.0**	**55**	**100.0**	**97**	**100.0**	**59**	**100.0**	**32**	**100.0**

Table 7 - Distribution Of Adenomyosis In Leiomyoma Cases

Lesion	Frequency	Percent
None	144	57.6
Adenomyosis	106	42.4
TOTAL	250	100.0

Table 7 Adenomyosis was present in 42.4% (106) of leiomyoma cases.

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Discussion

Leiomyoma is the most common myometrial lesion in this study with 48.6% of cases. Most of the studies showed leiomyoma as the most common presentation. Most cases of leiomyoma present with PV bleeding, dysmenorrhea, mass in the lower abdominal area, etc. Adenomyosis is a diagnosis made after a hysterectomy by histopathology. Since the symptoms of adenomyosis are vague it is undiagnosed unless hysterectomy specimens undergo histopathology tests. Within the uterus, the leiomyoma can be intramural, subserous, and submucous. [11] Cooke I D et al noted there were 75%, 10%, and 15% in their study group. In this study, 52.8% of cases showed intra-mural fibroids. 14.4% showed submucous regions, and 9.2% were subserous locations. Both in the submucous and intramural region was 10%, intramural and subserous were 8%, submucous and subserous were 2.4%, and all three locations were 3.2%. This finding goes in hand with the reference cited. In the current study, thirty percent (75) of the cases reported were associated with the early secretory phase. The percent of cases associated with the proliferative phase and late secretory phases was 20.8% (52) and 16% (40) respectively. The percent of cases associated with simple hyperplasia, disordered proliferative phase, and atrophic endometrium was 11.2% (28), 10.8% (27), and 9.6% (24) respectively. There was one (0.4%, total 2%) case of each - complex hyperplasia, Endometrial intraepithelial neoplasia, or endometrial carcinoma. If the myometrial tumor is large, the overlying endometrium may be thinned out. The atrophic endometrium was the most constant morphological change in the presence of submucous leiomyoma (83%). Atrophy is not only due to mechanical pressure but also from the hormonal insufficiency that occurs in the post-menopausal period.[12] In this study, the current study showed thinned-out endometrium of 0.1 to 0.2cm in 17.4% of subserosal leiomyoma, 13.9% of the submucous leiomyoma cases, and in 9.1% of intramural leiomyoma and very few cases of postmenopausal women. This should be further evaluated in detail. [13] Crum C P et al 1961 reported endometrial hyperplasia varied between 6% and 80%. Hyperplasia is the most common change in the endometrium with the fibroid uterus (Acta Ob. Gynec. 1963). Out of 390 hysterectomy specimens, 316 cases presented leiomyoma with different degrees of endometrial hyperplasia. Both leiomyoma and endometrial hyperplasia develop in the hormonal context. The most frequently occurring type is simple hyperplasia, suggesting that there is a rare progression to the highest grades. These features are due to the protective role of uterine leiomyoma. In the presence of leiomyoma, the endometrium undergoes host physiological as well as age-related changes.[14]Hyperplasia of the endometrium was recordable primarily in women with menopausal ovarian dysfunction In the current study, most of the cases were between 40 to 49 years. Of this age group, simple hyperplasia was seen in 10.6%. 22.9% showed a proliferative phase. 10.6% showed an early secretory phase. 40 cases belonged to ages more than 50 years.[15] In this study, out of 250 cases, 97 cases had an LMP of 16 to 30 days, and 39 cases had more than 30 days of LMP. Out of 250 cases, 30 cases showed a persistent proliferative phase with LMP for more than 15 days. 20 cases out of 250 cases with Simple Hyperplasia had LMP of more than 15 days. This showed unopposed estrogenic action (Hyper estrogenic stage). 20 cases showing atrophic endometrium were postmenopausal women. In the present study, leiomyoma associated with adenomyosis was noted in 22.0 % of cases. [16]The incidence of leiomyoma is almost equal to other data available in the world literature. Many of the endometrial changes noted also correlated with the findings of other authors. Many authors worked on the endometrial changes in leiomyoma.[17] A comparison with those studies revealed that the current observations were corroborative except for a few variations.[18]A striking observation was the association of adenomyosis and fibroid, 40% of uterine leiomyoma was associated with adenomyosis, which substantiates the hypothesis of hormonal dependency of these tumors. Persistent proliferative phase and simple hyperplasia were seen beyond 15 days of LMP. This means all these patients showed hyperestrogenic status, which also explains the various menstrual disturbances the patients present with. Reproductive failure may also be explained by these changes.[19,20]

Conclusion: In this study, most of the myometrial lesions(leiomyoma) were seen in the 4th and 5th decades of life. Intramural location was seen more than other locations. The endometrial changes seen

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were thinning hyperplasia(simple as well as complex) and infrequently carcinomatous change. The older group of women in this study had atrophic endometrium and relative changes. Many of the cases had persistent hyperestrogenic stimulus. Adenomyosis and my hyperplasia were frequent associations.

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