ORIGINAL RESEARCH

Adenomyosis and uterine bleeding: Clinicopathological correlation

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Abstract

Introduction: Adenomyosis is diagnosed histologically when benign endometrial glands and stroma are visualised penetrating the myometrium and surrounding myometrium being hypertrophic and hyperplastic. This condition can be asymptomatic or may be related to various clinical symptoms such as pain during menstruation (dysmenorrhea), heavy or prolonged menstrual bleed (menorrhagia) and pelvic pain. The association between adenomyosis and these clinical features singularly or in conjunction have been variably documented in previous studies.

Aims and Objectives: To evaluate depth and number of adenomyotic glands in myometrium and clinically correlate these with menorrhagia and dysmenorrhoea.

Materials and Methods: Hysterectomy specimen's received between August2022 and July2023 were reviewed along with relevant clinical details as per patient's record files. 82 samples with adenomyosis were included in the study after applying the inclusion and exclusion criteria. Depth of penetration of adenomyosis was categorized as Category1: upto inner 1/3rd of myometrium penetrated and Category 2: more than 1/3rd of myometrial thickness penetrated, from endometrial surface. The average numbers of adenomyotic glands per low power field (x 40 magnification), were calculated as an average of five fields with maximum glandular distribution were grouped as Group 1: 1-3 glands/ LPF and ≥ 3 glands/LPF. Relationship between these parameters and menorrhagia and dysmenorrhoea was evaluated. All the statistical analysis were done using spss software ver 22.0 the results were considered significant when *p* value was <0.05.

Results: The study included 82 hysterectomy samples, as per inclusion and exclusion criteria.Presence of menorrhagia significantly correlated with depth of endometrial glandular invasion into myometrium (p =0.001) with menorrhagiabeing present in 28%category 1 invasion and 66% in category 2 invasion. Dysmenorrhea was documented as presenting complaint in 24% of women in category 1 vs 47% in category 2, with significant correlation. (p=0.046). Menorrhagia also significantly correlated with average number of adenomyotic glands per low power field (p=0.001), menorrhagia being present in 28 cases with ≥ 3 adenomyotic glands/LPF and 17 cases of 1-3 glands/ LPF, however there was no significant correlation between dysmenorrhea and average number of adenomyotic glands (p=0.064).

Conclusion: Menorrhagia and dysmenorrhoea both correlated with the level of myometrial involvement by adenomyosis suggesting that the deeper the myometrium is penetrated the more are the symptoms. Menorrhagia also showed significant positive correlation with glandular density however dysmenorrhoea was independent of number of glands in the myometrium.

Keywords: Adenomyosis, Menorrhagia, Dysmenorrhoea, Depth of myometrial invasion, Number of adenomyotic glands/LPF

Introduction

Adenomyosis is diagnosed histologically when penetration of benign endometrial glands and stroma are visualised in myometrium and surrounding myometrium being hypertrophic and hyperplastic [(1)]. Carl Von Rokitansky first time described this finding

as "Cystosarcoma adenoids uterium"[2].Many theories have been proposed related to its pathogenesis, the most accepted one postulated that disruption of endometrium myometrium transition zone leads to its occurrence. The association between adenomyosis and symptoms such as heavy menstrual bleed, dysmenorrhea and pelvic pain have been variably documented in various studies[3,4,5]. Also it has been observed that there are no specific symptoms which can be related to this disease [6].

Aim: To evaluate depth of adenomyosis in myometrium and number of adenomyotic glands per low power field and clinically correlate these with menorrhagia and dysmenorrhoea.

Materials and Methods

Medical records were searched for women who underwent hysterectomy between October 2022 and September 2023 and hysterectomy samples were submitted for histopathological evaluation in department of Pathology at this institution. Details pertaining to age, parity, presenting complaints (dysmenorrhea, menorrhagia and pelvic pain) and hormonal status (Follicular Stimulating Hormone, Luteinizing Hormone, Prolactin, Thyroid Stimulating Hormone, Estriol and Progesterone) were noted from medical records. The cases were segregated according to inclusion and exclusion criteria.

Inclusion Criteria: 1.Well preserved formalin fixed hysterectomy specimens 2.Complete histopathological examination requisition forms with respect to age, parity, presenting complaints (dysmenorrhea, menorrhagia and pelvic pain), hormonal status and radiological findings, if any.

Exclusion criteria:1.Hysterectomy done in puerperium (6 weeks post birth/abortion) or during child birth. 2. Hysterectomy done for radiologically confirmed fibroids. 3. Hysterectomy specimens in which forms were incomplete with respect to above details. 4. Hysterectomy specimens which were not preserved in 10% neutral buffered formalin and grossly observed degenerative changes were present 5. Hysterectomy specimens which on gross examination showed visible fibroids and on microscopic examination showed abnormalities of endometrium attributed to other pathologies (hyperplastic endomerium, endometrium influenced by hormonal changes, neoplastic endometrium).

The specimens were evaluated for gross and microscopic examination. Uterus was cut longitudinally and fixed in 10% formalin. Gross evaluation was done for assessing visible foci of adenomyosis. Sections were taken from each specimen depending upon the gross appearance and stained with Haematoxylin and Eosin stain according to standard protocols. The stained sections were studied for the presence of adenomyosis which was defined as endometrial glands and/or stroma visualised at least 2.5mm below the endomyometrial junction [7].

Depth of penetration was classified as Category 1: upto inner 1/3rd of myometrium penetrated and Category 2: more than 1/3rd of myometrial thickness penetrated, from the endometrial side of the uterine cavity.

Adenomyotic glands per low power field were counted as an average of five fields with maximum glandular distribution for each case using formula ($n_1 + n_2 + n_3 + n_4 + n_5/N$) Where n was number of adenomyotic glands in one low power field (X 40 magnification) and N was total number of fields evaluated for calculation of average number of adenomyotic glands which were grouped asGroup 1: 1-3 glands/ LPF and $\geq$ 3 glands/LPF.

The sections were reviewed individually by two pathologists and there was no discordance in counting the number of glands. Dysmenorrhoea and menorrhagia were documented and correlated as per patient's clinical history obtained from patient record files. Menorrhagia was defined by heavy menstrual bleed and or prolonged menstruation[8]. Requirement of analgesics during menstruation was considered for defining dysmenorrhoea.The above two clinical findings were noted in clinical details by the clinician concerned and werespecifically requested for in the histopathological request form.

All the statistical analysis were done using spss software ver 22.0 the results were considered significant when p value was <0.05.

Results

A total of 567 women underwent hysterectomy in this hospital during our study period, out of which 67 specimens were not received in the histopathology laboratory. 20 specimens showed grossly degenerative changes and for 18 cases completely filled forms or clinical details as per our criteria were not available. 30 hysterectomies were done as cesarean hysterectomies or during period of puerperium and were excluded. Histological diagnosis rendered on remaining 432 specimens of uterus and cervix were leiomyoma alone in 266 cases, leiomyoma with concomitant adenomyosis in 44 casesand 40 cases which had a defined endometrial pathology (atrophic and related changes in 15 cases, hormonal induced changes in 6 cases,hyperplastic 14 cases andadenocarcinoma in 5 cases). The final cohort of cases included in the study was 82 cases where adenomyosis alone, was the significant histopathological finding and was grossly visible in 15 cases. (Figure 1).

Majority of patients undergoing hysterectomy were post-menopausal females with completed family.The age range of patients was 40-54 years with mean age of 48.9 and 50.6 years in category 1 and category 2 respectively. Overall mean parity 2.6 and category wise it was 2.8 and 2.5 in category 1and 2

respectively. Dysmenorrhoea and menorrhagia alone were the presenting complaint in 45 and 33 cases, respectively and 4 cases showed both the complaints, where adenomyosis was the only histopathological finding. (Figure 2).

In 25 cases less than 1/3 of thickness of myometrium was involved by adenomyosis (Category 1) whereas cases with more than one third myometrial involvement were 57 (Category 2). Presence of menorrhagia significantly correlated with depth of endometrial glandular invasion into myometrium (p =0.001) with menorrhagiabeing present in 28%cases of category 1 invasion and 66% in category 2 invasion(Table 1) Dysmenorrhoea also positively correlated with depth of myometrium penetrated and waspresenting complaint in 24% of women in category 1 vs 47% in category 2. (Table 2).

Presence of menorrhagia significantly correlated with average number of adenomyotic glands per low power field. Menorrhagia was present in 28 cases with ≥ 3 adenomyotic glands/LPF and 17 cases of 1-3 glands/ LPF (Table 3) whereas no significant correlation was obtained between average number of adenomyotic glands and dysmenorrhea (Table 4).

Table 1	Less than one third ofmyometrial thicknessinvolved	Greater than one third of myometrial thickness involved	Marginal Row Totals
Menorrhagia Present	7(13.72)[3.29]	38(31.28)[1.44]	45
Menorrhagia Absent	18(11.28)[4]	19(25.72)[1.76]	37
Marginal Column Totals	25	57	82 (Grand Total)

The chi-square statistic is 10.4927. The p-value is .001198. Significant at $p < .05$.

Table 2	Less than one third of myometrial thickness involved	Greater than one third of myometrial thickness involved	Marginal Row Totals
Dysmenorrhea present	6(10.06)[1.64]	27(22.94)[0.72]	33
Dysmenorrhea absent	19(14.94)[1.1]	30(34.06)[0.48]	49
Marginal ColumnTotals	25	57	82 (Grand Total)

The chi-square statistic is 3.9462. The p-value is .046978. Significant at $p < .05$

Table 3	1-3 glands/LPF	≥3 glands/LPF	Marginal Row Totals
Menorrhagia Present	17(24.15)[2.12]	28(20.85)[2.45]	45
Menorrhagia Absent	27(19.85)[2.57]	10(17.15)[2.98]	37
Marginal Column Totals	44	38	82 (Grand Total)

The chi-square statistic is 10.1148. The p-value is .001471. Significant at $p < .05$.

Table 4	1-3 glands/LPF	≥3 glands/LPF	Marginal Row Totals
Dysmenorrhea present	12(16.1)[1.04]	21(16.9)[0.99]	33
Dysmenorrhea absent	28(23.9)[0.7]	21(25.1)[0.67]	49
Marginal Column Totals	40	42	82 (Grand Total)

The chi-square statistic is 3.4078. The p-value is .064889. Not significant at $p < .05$

Fig 1: Showing grossly evident adenomyosis

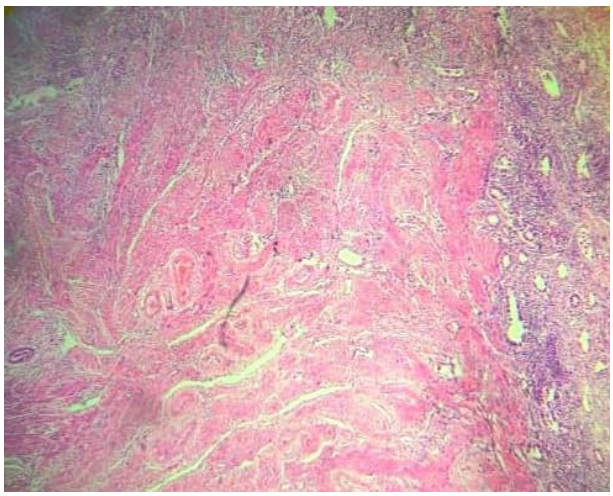

Fig 2: Microscopic adenomyosis, endometrial glands in Myometrium which appears hyperplastic (Hematoxylin& Eosin x 40)

Discussion

The diagnosis of adenomyosis using clinical criteria or international classification of diseases (ICD) 9, accurately diagnosed nearly a79% of incident and confirmed cases [(9)]. Similarly applying different histological criteria for sampling of uterine myometrial tissue, it was found that cases of adenomyosis doubled when number of sections was increased from 3 to 6 extra sections per uterus[(10)]. Such is the diversity in reporting the prevalence of adenomyosis that analysing data from 15 different hospitals and 25 different pathologists, the prevalence ranged from 12% to 58% across hospitals and from 10% to 88% across pathologists [(11)]. Similarly in our study when denominator was total hysterectomies done in one year period then average prevalence per year was 14.5% and when denominator was total hysterectomy specimens which underwent histopathological evaluation and where adenomyosis alone was the significant histopathological diagnosis was taken as numerator, the prevalence increased to 19%, both the findings being in conjunction with previous studies.

Most of the previous studies have documented median age of women with adenomyosis above 40 years, most common being 41-45 years age group with highest and lowest recorded mean for age being 54 and 37 years, respectively [(12)]. In our study the age range of patients undergoing hysterectomy was 40- 54 years and mean age of diagnosis of adenomyosis was 46.4 years. This was attributable to social stigma present in rural females in reporting gynaecological problems or seeking professional medical health care. The second reason being completing the family and avoiding hysterectomy, before pre or perimenopausal age, when symptoms become unbearable or untreatable apart from surgery.

The clinical features attributable to adenomyosis are menorrhagia or abnormal uterine bleeding; dysmenorrhea or pelvic pain, dyspareunia Infertility with uterine fibroids and endometriosis being related conditions [(9)] and these features can also be seen with other pathologies ranging from benign conditions like leiomyomas to malignant carcinomas, so histopathological evaluation has been the gold standard in diagnosis [(9,12)]. Adenomyosis is usually found with other pathological conditions, frequently with leiomyoma. We found 34.8% of cases of adenomyosis with concomitant leiomyoma. This is in agreement with previous published findings [(13,14)].In the present study we have excluded cases of adenomyosis in which leiomyoma were present however Levgur *et al* demonstrated that adenomyosis alone can cause symptoms related to abnormal uterine bleeding with or without concomitant leiomyoma[(3)]. This was similar to previously published literature where adenomyosis alone was cause of menorrhagia and dysmenorrhoea (alone or together) in 65% of cases and with concomitant leiomyoma in 35% of cases, when taken together.

The classic presentation of adenomyosis has been described as heavy painful uterine bleeding in a multiparous women above 40 years of age with heavy bleeding occuring in 40-60%of patients[(15)]. The amount of bleeding and degree of pain were shown to be significantly correlated with the degree of myometrial invasion [(16)]. So we designed our study to be limited in the sense that we did not assessed severity of menorrhagia but just recorded its presence or absence by objective questioning and we found thatthe severity of depth of adenomyotic invasion when greater than 1/3 of myometrial as measured from endometrial surface significantly correlated with presence of menorrrhagia. The same conclusion with respect to severity of menorrhgia and depth of myometrial invasion was documented by Levgur*et al*. [(3,17)]. The presence of menorrhagia also significantly correlated with mean number of adenomyotic glands/ LPF in the present study. However in a previous study number of adenomyosis foci per slide showed no

statistical difference when women with presence and absence of menorrhagia were compared [5].The significant association of mean number of glands being greater than 3 with presence or absence of menorrhagia in our study was in contrast to previous studies [3,5] the most probable reason being that adenomyotic glands when counted in our study design may have been present in deeper areas of myometrium with greater number and distribution, when sampling was done for histopathological evaluation.

An initial study by Bird *et al* demonstrated a significant correlation between severity of dysmenorrhoea which was present in only 4.3% of women when adenomyosis was limited to subendometrial basalis layer but the percentage drastically increased to 42.4 and 83.3 percent when adenomyosis extended to involve the mid and outer myometrium, respectively [10]. This was comparable to our results where dysmenorrhoea was present in 24% of cases win Category 1 but significantly increased to 47% in Category 2. However, a study by Sammour *et al* contrasted to our results in which dysmenorrhea did not correlated with degree of myometrial penetration[5].

We also found a significant positive correlation between depth of myometrium involvement and presence of dysmenorrhea as more number of women presents with dysmenorrhea when > 1/3 of myometrium is penetrated than the numbers of women when depth of penetration was <1/3 rd. However, Sammour A *et al* did not find significant correlation between dysmenorrhoeaand depth of penetration but they found a significant correlation with spread of adenomyosis in the myometrium [5]. A similar study by Nishida *et al* where they found that there was no correlation between glandular density which they counted as mean number of glands with dysmenorrhoea [4] corroborated by our study.

Conclusion

Adenomyosis is a condition which primarily affects multiparous females in pre, peri and post-menopausal age group. Menorrhagia and dysmenorrhoea both positivelycorrelatedwith the level of myometrial involvement by adenomyosis suggesting that the deeper the myometrium is penetrated the more are the symptoms. Menorrhagia also showed significant positive correlation with glandular density however dysmenorrhoea was independent of number of glands in the myometrium.

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