Clinical symptoms and histopathological findings in subjects with adenomyosis uteri

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Summary

Objective: The purpose of this study was to compare the clinical symptoms and histopathological findings in subjects with adenomyosis uteri. *Method*: Infiltration depth and spread of adenomyotic foci together with clinical symptoms and findings were compared in a total of 103 subjects who had undergone hysterectomy and were diagnosed with adenomyosis uteri through histopathological examinations. *Results:* The spread of adenomyotic foci in myometrial tissues was observed to significantly increase as the depth of myometrial infiltration increased in subjects with adenomyosis ($p < 0.05$). It was observed that there was significantly higher myometrial infiltration depth in subjects with dysmenorrhea and severe anemia, and diffuse adenomyotic foci in subjects with menometrorrhagia ($p < 0.05$). *Conclusion*: Increased infiltration depth and spread of adenomyotic foci in myometrial tissues in subjects with adenomyosis uteri were studied. When clinical symptoms and findings in subjects with adenomyosis, such as dysmenorrhea, anemia and menometrorrhagia are compared with these histopathological findings, infiltration depth and spread of adenomyotic foci appear to determine the clinical severity of adenomyosis.

Key words: Adenomyosis uteri; Symptoms; Histopathology.

Introduction

Adenomyosis refers to the presence of islands of endometrial glands and stroma within the myometrium [1]. However, two important issues have to be mentioned within this description: 1) that the adenomyotic site is located away from the endometrial-myometrial junction at a distance further than 25% of full myometrial thickness, and 2) this site is surrounded by a myometrial hypertrophy, which does not exist at the endometrial-myometrial junction [2].

Symptoms associated with adenomyosis, such as dysmenorrhea, menometrorrhagia, dyspareunia and chronic pelvic pain have been considered to be related to adenomyotic foci within the myometrium. Although symptoms associated with adenomyosis such as dyspareunia, menstrual irregularities and pelvic pain are believed to be related to the depth of adenomyotic tissue within the myometrium, results of the studies on this topic are contradictory [3-6].

Recently interest on adenomyosis has increased because of the results of recent studies in which adenomyosis was reported to have similar symptoms to endometriosis, such as pelvic pain, dysmenorrhea and bleeding disorders, as well as being involved in etiologies of infertility and early abortion. However, the number of studies on adenomyosis is rather less when compared with those on endometriosis. In this study we aimed to investigate the comparison of clinical symptoms and histopathological findings in women with adenomyosis.

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Method

A total of 103 subjects who had undergone abdominal, vaginal or laparoscopic hysterectomy with or without salpingo-oophorectomy between October 2003 and April 2004 in our clinic, and were diagnosed with adenomyosis through histopathological examination were included in this study. Written informed consent was obtained from each woman before surgery and the consent forms and protocols were approved by the Human Investigation Committee of Ege University.

The uterus specimens obtained through hysterectomy were weighed, followed by full-thickness cross-sections obtained from anterior, posterior and lateral walls for histopathological examination.

Adenomyosis was defined as the presence of endometrial glands and stroma within the myometrium, at least 2 mm below the endometrial-myometrial junction, and in the presence of surrounding myometrial hyperplasia. All histopathologic specimens were examined by a pathologist who was not aware of the clinical diagnoses of the patients. To study the relationship between myometrial infiltration depth and symptomatology, the patients were stratified according to the myometrial infiltration depth, which defines the extent of invasion of adenomyotic foci with respect to myometrial thickness, into four groups. Group A (n: 34) consisted of specimens with adenomyosis penetration of < 25%, group B (n: 27) 26-50%, group C (n: 28) 51-75%, and group D (n: 14) > 75% of myometrial thickness.

The spread of adenomyosis foci, which defines the intensity of adenomyosis, was assessed by studying the number of foci per slide, and less than four adenomyotic sites were accordingly defined as focal adenomyosis, while four or more adenomyotic foci were defined as diffuse adenomyosis.

The infiltration depth and spread of adenomyotic foci were evaluated according to epidemiological factors, such as menopausal status, duration of reproductive period, parity, and

smoking habits; early pregnancy loss and infertility; symptoms such as bleeding disorders, chronic pelvic pain, dysmenorrhea and dyspareunia; history of previous uterine surgery, anemia and gynecological conditions accompanying adenomyosis.

The study data were statistically analyzed using SPSS software. The chi-square test was used for the comparison of categorical values, while a special test, namely Fisher's exact test was used when the tables were in a 2 x 2 situation. Significance was determined as $p < 0.05$.

Results

The infiltration depth and spread of adenomyotic foci in 103 subjects is presented in Table 1. It can be seen that the rate of diffuse adenomyotic foci within myometrial tissue showed a significant increase together with the myometrial infiltration depth ($p < 0.05$).

Patient characteristics and symptoms are summarized in Table 2. The mean age of all women was 50.3 ± 10.4, and no significant difference was observed between age, infiltration depth and spread of adenomyotic foci in subjects with adenomyosis (Table 1).

Due to the estrogen effect on the etiopathogenesis of adenomyosis, the "cumulative time" with estrogen effect was calculated by considering the total duration of the reproductive periods of subjects, and the mean value of the duration of the reproductive period was determined as 33.91 ± 13.3 years in patients with adenomyosis (Table 2). Although it was not significant, spread of adenomyotic foci was found to be higher in subjects who had a longer duration of the reproductive period, while no significant difference was observed between the total duration of reproductive period and depth of infiltration (Table 3).

Table 1. — *Relationship between depth of infiltration and spread of adenomyotic foci*.

	Infiltration depth of adenomyotic foci (n: 103)	Spread of adenomyotic foci	
		Focal (n: 47)	Diffuse (n: 56)
Group I	34 (34.0%)*	30 (63.8%)*	4 (11.8%)*
Group II	27 (26.0%)*	11 (23.4%)*	16 (59.8%)*
Group III	28 (27.0%)*	4 (14.3%)*	24 (85.7%)*
Group IV	14 (13.6%)*	2 (14.3%)*	12 (85.7%)*

*p < 0.05.

Table 2. — *Summary of patient characteristics and symptoms*.

Patient characteristics	Adenomyosis (n: 103)
Age (years)	50.3 ± 10.4
Reproductive period (years)	33.91 ± 13.3
Menopause (%)	31 (30.1%)
Oligomenorrhea (%)	4 (3.9%)
Regular menstruation (%)	21 (20.4%)
Nulliparous (%)	22 (21.4%)
Smoking (%)	37 (35.9%)
History of previous uterine surgery (%)	63 (61.2%)
One previous uterine surgery (%)	24 (23.2%)
Two previous uterine surgeries (%)	28 (27.2%)
Three previous uterine surgeries (%)	9 (8.7%)
Four previous uterine surgeries (%)	1 (1%)
Primary infertility (%)	2 (1.9%)
Secondary infertility (%)	5 (4.6%)
Early pregnancy loss (%)	11 (10.67%)
Anemia (%)	22 (21.4%)
Severe anemia (%)	5 (4.9%)
Blood transfusion (%)	14 (13.6%)
Symptoms	
Menometrorrhagia (%)	47 (45.6%)
Pelvic pain (%)	33 (32.04%)
Dysmenorrhea (%)	26 (25.2%)
Dyspareunia (%)	19 (18.4%)

Table 3. — *Symptoms, myometrial infiltration depth and spread of adenomyotic foci*.

	Infiltration depth of adenomyotic foci (n: 103)			Spread of adenomyotic foci (n: 103)		
	Group I (n: 34)	Group II (n: 27)	Group III (n: 28)	Group IV (n: 14)	Focal (n: 47)	Diffuse (n: 56)
Reproductive period (years)	33.88	33.52	34.36	33.86	33.68	34.11
Menometrorrhagia n: 47 (%)	12 (35.3%)	12 (44.4%)	15 (53.9%)	8 (57.1%)	14 (29.8%)*	33 (58.9%)*
Pelvic pain n: 33 (%)	7 (20.6%)*	6 (22.23%)*	9 (32.14%)*	11 (78.57%)*	14 (29.78%)	19 (33.93%)
Dysmenorrhea n: 26 (%)	6 (17.6%)*	7 (25.9%)*	5 (17.9%)*	8 (57%)*	10 (21.3%)	16 (28.6%)
Dyspareunia n: 19 (%)	5 (14.7%)	5 (22.7%)	5 (21.7%)	4 (28.5%)	8 (17.0%)	11 (19.6%)

*p < 0.05.

Thirty-three patients (32.04%) complained of pelvic pain (Table 2). The infiltration depth of adenomyotic foci was significantly higher in these subjects ($p < 0.05$; Table 3).

When the subjects were evaluated with respect to their menstrual patterns, regular menstruation was found in 21 patients (20.4%), menopause in 31 patients (30.1%), menometrorrhagia in 47 patients (45.6%), and oligomenorrhea in four patients (3.9%) (Table 2). Diffuse adenomyotic foci were significantly higher in subjects with menometrorrhagia ($p < 0.05$; Table 3). Although not significant, infiltration depths of adenomyotic foci were found to be higher in women with menometrorrhagia.

Dysmenorrhea was observed in 26 patients (25.2%), while dyspareunia was observed in 19 patients (18.4%) (Table 2). Infiltration depth was found to be significantly higher in women with a history of dysmenorrhea ($p < 0.05$; Table 3) whereas the rates of diffuse adenomyotic foci were insignificantly higher in these women. No significant difference was found between dyspareunia, infiltration depth, and spread of adenomyotic foci. However, dyspareunia was determined to be more common in women with higher infiltration depth (groups C and D) and diffuse adenomyotic foci (Table 3).

When the subjects were evaluated with respect to parity, it was found that 22 subjects (21.4%) were nulliparous (Table 2). The difference between parity, infiltration depth, and spread of adenomyotic foci was not significant. However, the rate of diffuse adenomyotic foci observed in multiparous subjects was higher than that in nulliparous women (58% vs 42%, respectively).

Rate of smoking was found as 35.9% (37) among subjects (Table 2). Although not significant, it was observed that smoking was related to lower myometrial infiltration depth (groups A and B) and higher rates of focal adenomyotic foci ($p > 0.05$).

It was found that 63 (61.2%) of the subjects had a history of previous uterine surgery, such as pregnancy evacuation, uterine curettage and cesarean section, which would have a traumatic effect on the endometrial-myometrial junction (Table 2). Previous cesarean section, transcervical endometrial curettage or uterine evacuation were recorded only if performed more than six months prior to hysterectomy. The rate of diffuse adenomyotic foci with a high infiltration depth (groups C and D) was observed to be insignificantly higher in subjects with a history of previous uterine surgery. No significant difference was found between the number of previous uterine surgeries, spread, and infiltration depth of adenomyotic foci (Table 4).

Table 4. — *Number of previous uterine surgeries in subjects with adenomyosis*.

No. of previous uterine surgeries	Infiltration depth of adenomyotic foci (n: 103)				Spread of adenomyotic foci (n: 103)		p
	Group I (n: 34)	Group II (n: 27)	Group III (n: 28)	Group IV (n: 14)	Focal (n: 47)	Diffuse (n: 56)	
0 (n: 41)	17 (50%)	8 (29.63%)	12 (42.85%)	4 (28.6%)	20 (42.5%)	20 (35.7%)	> 0.05
1 (n: 24)	6 (17.6%)	10 (37%)	4 (14.28%)	4 (28.5%)	11 (23.4%)	13 (23.2%)	> 0.05
2 (n: 28)	9 (26.5%)	7 (25.9%)	6 (21.4%)	6 (42.85)	12 (25.5%)	17 (30.4%)	> 0.05
3 (n: 9)	2 (5.9%)	2 (7.4%)	5 (17.9%)	–	4 (8.5%)	5 (8.9%)	> 0.05
4 (n: 1)	–	–	1 (3.6%)	–	–	1 (1.8%)	> 0.05

Table 5. — *Indications for hysterectomy*.

Indications for hysterectomy	No. (%)
Myoma uteri	47 (46%)
Associated gynecological conditions*	15 (14%)
Endometrial hyperplasia	13 (12%)
Uterine prolapse	6 (6%)
Adnexal mass	5 (5%)
Endometrial carcinom	5 (5%)
Menometrorrhagia+	4 (4%)
Pelvic pain	3 (3%)
Cervical dysplasia	3 (3%)
Other gynecological malignancies	2 (2%)

*: patients having more than one indication (myoma uteri, endometrial hyperplasia, menometrorrhagia, adenomyosis, endometriosis, adnexal mass, pelvic pain); +: medical therapy-resistant.

Table 6. — *Histopathological findings of subject*.

Histopathological findings	No. (%)
Adenomyosis + myoma uteri	52 (50.48%)
Pure adenomyosis	25 (24.27%)
Adenomyosis + endometrial hyperplasia	9 (8.74%)
Adenomyosis + endometrial carcinom	5 (4.85%)
Adenomyosis + endometriosis	3 (2.91%)
Adenomyosis + benign adnexal mass	3 (2.91%)
Adenomyosis + endometrial polyp	2 (1.9%)
Adenomyosis + cervical dysplasia	2 (1.9%)
Adenomyosis + other gynecological malignancies	2 (1.9%)

When we evaluated the women with respect to their infertility histories, we observed that two (1.9%) subjects had primary and five (4.6%) subjects had secondary infertility (Table 2). Eleven subjects (10.67%) had a history of early pregnancy loss (Table 2). Although not significant, spread and infiltration depth of adenomyotic foci were observed to be higher in women with a history of early pregnancy loss and infertility.

Anemia (hgb level < 12 g/dl) due to menometrorrhagia was observed in 27 patients (26.3%) (Table 2). No significant difference was observed between anemia, spread, and infiltration depth of adenomyotic foci. During the preoperative period, 14 subjects required a blood transfusion due to severe anemia (hgb level < 10 g/dl) (Table 2). Infiltration depth of adenomyotic foci was significantly related to preoperative requirement of blood transfusion ($p < 0.05$), where no significant difference was observed between the spread of adenomyotic foci and preoperative requirement of blood transfusion.

Indications for hysterectomy and histopathological findings in descending order of frequency are shown in Tables 5 and 6, respectively. According to the results of histopathological examinations, 25 (24.3%) out of 103 subjects had pure adenomyosis, while the remaining 78 subjects with adenomyosis had other associated gynecological conditions. The results obtained with histopathological examination of the subjects were in accordance with the operation indications, where myoma uteri was the most common histopathological diagnosis (52 subjects; 50.48%). The rate of diffuse adenomyosis was higher in subjects with pure adenomyosis than in subjects with adenomyosis-associated gynecological conditions, but the difference was not significant. The prevalence of endometriosis was 2.91% [3].

The mean uterus weight was 222.23 g in 103 subjects, whereas mean uterus weight in 25 (24.3%) subjects with pure adenomyosis and in 78 subjects with adenomyosis-associated gynecological conditions was 153.09 g and 242.31 g, respectively ($p < 0.05$). No significant difference was found between uterus weight, infiltration depth and spread, which determine the severity of the disorder.

Discussion

The mean age of women with adenomyosis has been reported to be between 40 and 60 years [7-9]. In a study where magnetic resonance imaging (MRI) was used for the evaluation of infertility, adenomyosis was most frequently seen in women in the second and third decades [10]. It has been reported that incidence of adenomyosis was about 17% in women who had undergone hysterectomy following cesarean section [11].

This study included women who had histopathologically confirmed adenomyosis. The mean age of the women was 50.3, which was also the average age group for hysterectomy operations. Through advancement and extensive use of alternative diagnostic methods for adenomyosis, apart from histopathological examination of hysterectomy material, the age groups in which adenomyosis is more frequently seen could be more accurately determined with MRI.

Adenomyosis is a condition in which ectopic endometrial glandular and stromal structures are embedded within the myometrium, while surrounded by a hyperplastic and hypertrophic myometrium layer. Symptoms associated with adenomyosis such as dysmenorrhea, menometrorrhagia, dyspareunia and chronic pelvic pain

have been considered to be related to adenomyotic foci within the myometrium. The spread of these foci has been reported to be related to myometrial invasion depth in several studies [3, 4]. In the present study, the rate of diffuse adenomyotic foci with higher myometrial infiltration depth (groups C and D) showed a significant increase.

The results of immunohistochemical studies emphasize the influence of estrogen and progesterone on the etiology of adenomyosis [1, 12-15]. This hypothesis is supported by the fact that adenomyosis can be associated with pathologies such as leiomyoma, endometrial hyperplasia, endometrial cancer and endometrial polyps which are considered to have an estrogen effect in their etiology [7, 8, 16]. Similarly in this study, pure adenomyosis was observed in only 25 (24.3%) out of 103 adenomyotic cases. We observed that women with adenomyosis-associated gynecological conditions had diffuse adenomyotic foci with a higher infiltration depth (groups C and D) (in which the etiopathogenesis high estrogen activity is known to play a role, such as myoma uteri, endometrial polyps, endometrial hyperplasia and endometrial cancer, when compared with subjects with pure adenomyosis).

Although adenomyosis is generally associated with other gynecological conditions such as leiomyoma and endometrial hyperplasia, which are known to be related to high levels of estrogen, it is rarely seen together with endometriosis. This finding supports the idea that endometriosis and adenomyosis are two distinct pathologies [8, 17, 18]. Similarly in this study, pure adenomyosis was observed in only 24.27% [25] of the cases, while the most common histopathologic findings accompanying adenomyosis were descendingly ordered as myoma uteri 50.48% (52), endometrial hyperplasia 8.74% (9), endometrial cancer 4.85% (5), endometriosis 2.91% (3) and endometrial polyps 1.9% (2).

It has been suggested that early menarche, late menopause and bleeding disorders are related to adenomyosis. However, contradictory results have been reported in different studies. Some authors suggest that there is no relationship between adenomyosis and menstrual cycle patterns, age of menarche and menopause [7], while others believe that there is a strong correlation between adenomyosis and menstrual patterns [8].

The relation between total duration of the reproductive period and adenomyosis was evaluated in this study. Although duration of the reproductive period might be affected by conditions such as obesity, medications and pregnancy, it is the parameter that shows the whole period where the hormonal effects under suspicion in etiology do exist. High infiltration depth of of adenomyotic foci (groups C and D) was observed in women with longer reproductive periods. Additionally, low infiltration depth of adenomyotic foci (groups A and B) were determined in women where adenomyosis was not associated with any other gynecological conditions related to estrogen effects. These findings, which seem to support each other, were not significant.

Subjects with adenomyosis are reported to be asymptomatic with a rate of 35%. The most commonly observed findings, which are termed the adenomyosis triad, consist of menorrhagia (50%), dysmenorrhea (30%), and sensitive, symmetrically expanded uteri. Other less commonly seen symptoms that follow may be dyspareunia and chronic pelvic pain. These symptoms observed in adenomyosis are non-specific symptoms, and are also seen in gynecological conditions that may be associated with adenomyosis [12].

The reasons for menorrhagia in subjects with adenomyosis include impaired uterus contractions during menstruation due to affected myometrium, increased endometrial surface area, excessive secretion of prostaglandin and hyperestrogenism, while uterine irritability secondary to blood loss and pseudodesidual edema occurring around adenomyotic foci are reported to be causes of dysmenorrhea [4].

The most commonly observed symptoms in subjects with adenomyosis were menometrorrhagia, pelvic pain, dysmenorrhea, and dyspareunia in this study. There are many studies where the relationship between symptoms associated with adenomyosis and prevalence of the disorder and infiltration depth within the affected site have been investigated. It was reported that frequency of dysmenorrhea was directly related to infiltration depth [5, 6], while the extent of adenomyosis was correlated with dysmenorrhea-related menorrhagia with respect to spread and infiltration depth [4] in these studies.

A significant relationship was observed between infiltration depth and menometrorrhagia, and between infiltration depth and dysmenorrhea in this study. The rate of adenomyotic foci with high infiltration depth was significantly increased in subjects where a preoperative blood transfusion was required.

Adenomyotic foci do not consist of functional endometrium. However, a higher tendency for bleeding has been reported in adenomyotic foci with profound myometrial inhabitance, without any definitive explanation for this condition [19, 20]. This is in accordance with the findings in this study that there was a significantly high infiltration depth (groups C and D) in subjects who required blood transfusions during the preoperative period.

Contradictory results of studies where a relationship between symptoms and spread, and infiltration depth of adenomyotic foci in subjects were evaluated might be due to the fact that associated pathologies such as myoma uteri, endometrial hyperplasia, endometrial cancer and endometriosis were present with various frequencies in the women who took part in these studies.

It was reported that the uterus could reach a weight of 80-200 g in women with adenomyosis [12]. In a study where uterus weight was evaluated together with symptoms and histopathological findings, uterus weight in subjects only with adenomyosis was found to be significantly lighter than those in subjects with leiomyoma [21]. Mean uterus weight in subjects with adenomyosis was found as 222.23 g in this study. In subjects with pure adenomyosis and adenomyosis-associated gynecological

conditions, mean uterus weight was observed as 153.09 g and 242.31 g, respectively, $p < 0.05$. This difference, which is in accordance with the studies in the literature, appears to result from myoma uteri as an associated pathology. There was no significant relationship between uterus weight, infiltration depth and spread, which determine the severity of the disorder.

It has been reported in many studies that adenomyosis is more frequently seen in multiparous subjects [7-9, 16]. It was stated that aggressive trophoblastic activity during pregnancy could lead to an increase in adenomyotic sites within the myometrium, and this could also be predisposed by hormonal status during pregnancy [7].

In accordance with the literature, multiparous women were more frequently observed than nulliparous subjects with adenomyosis in this study (78.6% vs 21.4%, respectively). There was no significant difference between parity, spread and infiltration depth of adenomyotic foci, however, in accordance with the above-mentioned studies, in which prevalence of the disorder has been reported to increase during pregnancy, extensive adenomyosis was more frequently observed in multiparous subjects.

It has been stated that estrogen levels were lower in smokers, and accordingly adenomyosis was less commonly seen in smokers. Also the risks of myoma uteri and endometrial cancer were lower in smokers due to decreased levels of estrogen [7]. History of smoking was evident in 35.9% of the subjects with adenomyosis in this study. Although not significant, subjects who smoked had focal adenomyotic foci with a low infiltration depth (groups A and B). It seems to be characterized by focal adenomyotic foci and low infiltration depth (groups A and B) in smokers with adenomyosis.

There are studies where interferences such as early pregnancy termination and cesarean section are suggested to play a role in the etiology of adenomyosis and to cause iatrogenic weakness within the endometrial-myometrial junction, leading to invasion of endometrial glandular and stromal structures into the myometrium [2, 8, 17]. On the other hand, there are also studies where such interferences were shown to have no relationship with the development of adenomyosis [7]. The rate of subjects with a history of previous uterine surgery was found to be 61.2% in this study. Diffuse adenomyotic foci with high infiltration depth (groups C and D) were found in subjects with a history of previous uterine surgery. However, no significant differences were observed between the number of previous uterine surgeries and adenomyosis, with respect to both spread and infiltration depth of involvement.

The endometrial-myometrial junction consists of basal endometrium and subendometrial myometrium. This is the functional unit necessary for sperm transportation, embryonic implantation, placental development and menstruation [22]. Adenomyosis, whose etiology is considered to be effected by weakness in the endometrial-myometrial junction due to congenital or acquired factors [14-15, 23], might have a relationship with early abortions and infertility. Moreover, patients with adenomyosis have also been shown to have high levels of nitric oxide which have a negative effect on embryonic implantation and the spermatozoon [24, 25].

Today, considerable advancements through technological developments have been achieved in infertility and the average age for the first pregnancy has increased. Therefore, adenomyosis can be diagnosed during investigations for infertility. It was reported in one study that adenomyosis was diagnosed by using magnetic resonance imaging in 14 (53.8%) out of 26 patients who were being examined for infertility, menorrhagia and dysmenorrhea [22].

The subjects evaluated in this study were often multiparous patients in the fourth or fifth decades. Therefore, histories of infertility and early abortion were also investigated. However, subjects with a history of infertility or early abortion were rather few in number. Seven subjects (6.5%) had a history of infertility, while 11 (10.8%) had a history of early abortion. Diffuse adenomyotic foci with high infiltration depth (groups C and D) were found to be insignificant in these subjects with histories of early abortion and infertility.

As a result, the relationship between adenomyosis and conditions under discussion could be further cleared up with higher numbers of subjects included in studies [26].

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