Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(4): 989-993
doi: 10.52142/omujecm.39.4.13

Evaluation of mammographic features in women with adenomyosis

Nezaket KADIOĞLU[1,*], Ayçağ YORGANCI[2], Harika GUMGUMCU[2], M. Kuntay KOKANALI[2], Şebnem ÖZYER[2], Yaprak ENGIN USTUN[3]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Yüksek Ihtisas University, Ankara, Türkiye
[2]Department of Obstetrics and Gynecology, University of Health Sciences, Ankara City Hospital, Ankara, Türkiye
[3]Department of Obstetrics and Gynecology, University of Health Sciences, Etlik Zübeyde Hanım Women's Health Education and Research Hospital, Ankara, Türkiye

Received: 20.07.2022 • **Accepted/Published Online:** 05.08.2022 • **Final Version:** 29.10.2022

Abstract

This study aimed to investigate the mammographic features in women with adenomyosis to determine the relationship between adenomyosis and breast disease. In this study, the mammographic features of women with adenomyosis were recorded. For the control group, women who had mammography without any gynaecologic complaints and with normal pelvic ultrasound were selected. The adenomyosis group had higher breast density, more micro and macro calcifications, and higher BIRADS-mammography classification than the control group. When patients with low mammographic density (Density A - B, n = 80) and high mammographic density (Density C - D, n = 60) were compared, there were no statistically significant differences between the groups except the presence of adenomyosis. When patients were compared according to the BIRADS 1 - 2 (n=114) and BIRADS 3 - 4 (n=26) category, age ≥ 49.5, gravidity ≥ 3, parity ≥ 2, and the presence of adenomyosis were significantly higher in the BIRADS 3 - 4 category. In the logistic regression analysis, the presence of adenomyosis was found to be the sole factor for BIRADS 3-4 category. The results of our study suggested that patients with adenomyosis have an increased risk of higher mammographic breast density and BIRADS 3 classification.

Keywords: BIRADS, breast density, gynecology, mammography, uterine adenomyosis

1. Introduction

Adenomyosis is characterized by the presence of ectopic endometrial glands and stroma within the myometrium. Abnormal uterine bleeding, pelvic pain, and sub infertility are the typical symptoms of adenomyosis (1, 2). It is difficult to report the true prevalence of adenomyosis since histopathological confirmation is required although clinical symptoms and imaging modalities suggest adenomyosis. (3). Besides, leiomyoma and endometriosis that cause similar symptoms are often associated with adenomyosis (1, 4). The traditional belief of adenomyosis as a disease of multiparous women of perimenopausal age has begun to change with the awareness of the disease and the advances in diagnostic technologies (3). Nevertheless, most women who present with the full symptoms of adenomyosis require hysterectomy during the perimenopausal period.

The etiopathogenesis of adenomyosis has not been fully elucidated. Several factors have been suggested facilitating the invasion of the myometrium with the endometrial cells or transformation of Müllerian remnants to adenomyosis (5-7). Local sex steroid hormonal imbalance and inflammatory status are the main ones among these factors (5-7). Given that these factors are also involved in benign and malignant breast diseases (8, 9), we aimed to investigate the relationship between adenomyosis and breast disease. For this purpose, we evaluated the mammographic features in a cohort of women with histopathologically proven adenomyosis.

2. Materials and Methods

In this retrospective study, the histopathological records of women who had undergone hysterectomy in our Hospital between 2013-2017 were reviewed. Approval was obtained from the review board of the institution (10-11/2018). Patients who had clinically adenomyosis symptoms and histopathologically proven diagnosis of diffuse adenomyosis or adenomyoma were included in the study. Histopathological reports showing focal adenomyosis, uterine leiomyoma > 1cm in hysterectomy specimen, and other premalignant and malignant uterine, cervical or ovarian pathologies were excluded. Other exclusion criteria were patients with a history of local or systemic hormonal treatments due to adenomyosis symptoms, prior use of oral contraceptive pills, benign or

*Correspondence: nzkt81@gmail.com

malignant breast disease, breast biopsy, treatment or operation due to endometriosis. Demographic and clinical characteristics of patients who had mammograms with/without breast ultrasound (USG) six months before or after the hysterectomy were included in the analysis. Uterine volume was calculated according to the pelvic ultrasound measurements performed in the preoperative evaluation period. Endometrial biopsy results performed in the preoperative evaluation period were also recorded. The control group consisted of women who were admitted for routine gynaecologic follow-up. Inclusion criteria for the control group were women who had mammography and/or breast USG without any gynaecologic complaints and with normal pelvic ultrasound. Similarly, women with a history of benign or malignant breast disease, breast biopsy, treatment or operation due to endometriosis, and other malignant diseases were also excluded from the control group.

The Breast Imaging Reporting and Data System (BIRADS) is being used since 1993 for the standard reporting of breast pathology seen on mammograms and ultrasound (10). For mammography, the BIRADS lexicon includes the following principal headlines for reporting: 1) Breast density is the comparison of the fat tissue and fibroglandular tissue in the breast and classified as (A) if the breasts are almost entirely fatty; (B) if there are scattered areas of fibroglandular density; (C) if the breasts are heterogeneously dense, which may obscure small masses; and (D) if the breasts are extremely dense, which lowers the sensitivity of mammography. 2) Mass shape classified as oval, round, and irregular. 3) Calcifications are reported as benign, intermediate, and suspicious. 4) Architectural distortion 5) Asymmetries classified as asymmetry, global asymmetry, developing asymmetry, and focal asymmetry. 6) Intramammary lymph nodes 7) Skin lesions 8) Solitary dilated duct 9) Associated findings. 10) Location of the lesion. The features on mammography are categorized as BIRADS 0 to 6 according to benign and malign characteristics. The reports of mammography were reviewed for both study groups and the reported features were noted.

Data analysis was performed by the IBM SPSS Statistics version 22 program (SPSS, Chicago, IL, USA). The suitability of continuous variables to normal distribution was examined with the Shapiro-Wilk test. Since not all the variables were normally distributed, the values were given as median (min. – max.). The descriptive statistics of continuous variables were done by the Mann-Whitney test. The descriptors of the questionnaires were shown in numbers and percentages. Crosstables were created for the categorical variables and a Chi-square test was applied to investigate the intergroup differences. Data were analyzed at a 95% confidence level and $p<0.05$ was considered to be significant. The effects of the confounding variables to BIRADS 3-4 classifications were sought by logistic regression analysis. BIRADS 3-4 was the dependent variable. The area under the receiver-operating characteristics (ROC) curve was used to determine the cut-off values. The following predictors were examined: age < 49.5, and ≥ 49.5, gravidity < 3 and ≥ 3; parity < 2 and ≥ 2, and the presence of adenomyosis (yes or no). Odds ratios (OR) for the predictors including 95 % CI's were calculated.

3. Results

There were 70 patients in the adenomyosis group who met the inclusion and exclusion criteria. The flowchart of the adenomyosis group is shown in Fig. 1.

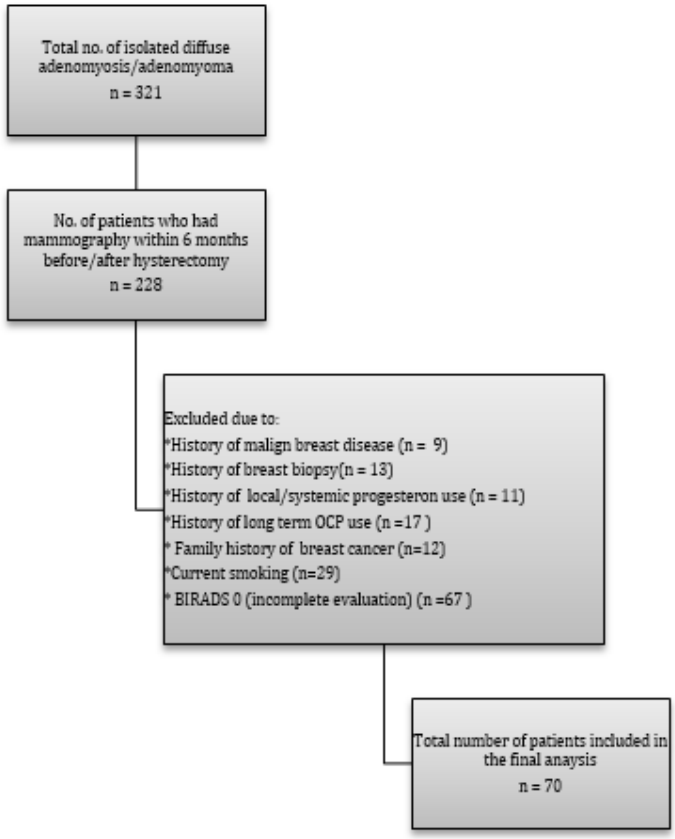

Fig. 1. Flowchart of the adenomyosis group

For the control group, 70 patients who met the criteria were selected from the routine follow-up patients. The demographic and clinical characteristics of the adenomyosis and the control groups are shown in Table 1. The median age of the adenomyosis group was significantly higher than the control group [49 (40-55) vs. 47 (41-55), $p = 0.012$; respectively]. While the number of gravidity, parity, and voluntary pregnancy terminations were significantly higher in the adenomyosis group than the controls, the BMI, age of menarche, and first birth were similar between groups. The median uterine volume was 177 (40-582) cm^3 in the adenomyosis group. Pathological reports of preoperative endometrial biopsies of the adenomyosis group revealed benign findings (30%), endometrial polyp (32.8%), endometrial hyperplasia without atypia (28.6%), and endometrial hyperplasia with atypia (8.6%).

Table 1. The demographic and clinical characteristics of the adenomyosis and the control group

	Adenomyosis group (n=70)	Control group (n=70)	P value
Age	49 (40-55)	47 (41-55)	**0.012**
BMI	30 (21-46)	30 (21-47)	0.9
Gravida	4 (0-8)	2 (0-10)	**< 0.001**
Parity	3 (0-6)	2 (0-7)	**< 0.001**
Abortus	0 (0-4)	0 (0-3)	0.13
D&C	0 (0-3)	0 (0-3)	**0.05**
Age of Menarche	13 (11-16)	13 (11-16)	0.53
Age at first birth	27 (17-35)	26 (17-35)	0.56
Uterine volume (cc)	177 (40-582)	N/A	N/A
Endometrial biopsy			
Benign	21 (30%)		
Endometrial polyp	23 (32.8%))		
Endometrial hyperplasia w/o atypia	20 (28.6%)	N/A	N/A
Endometrial hyperplasia w atypia	6 (8.6%)		

BMI: Body mass index; D&C: Dilation and curettage
P value <0.05, statistically significant

The mammographic findings of the adenomyosis and the control group are shown in Table 2. The adenomyosis group had higher breast density, more micro and macro calcifications, and higher BIRADS-mammography classification than the control group. All calcifications were reported as benign calcifications.

Table 2. Mammographic findings of the adenomyosis and the control group

	Adenomyosis group (n=70)	Control group (n=70)	P value
Breast density			
A	7 (10%)	11 (15.7 %)	
B	24 (34.3%)	38 (54.3 %)	**0.024**
C	27 (38.6%)	15 (21.4 %)	
D	12 (17.1%)	6 (8.6 %)	
Calcifications			
None	25 (35.7%)	45 (64.3%)	
Micro	24 (34.3%)	12 (17.1%)	**0.001**
Macro	8 (11.4%)	10 (14.3%)	
Micro + Macro	13 (18.6%)	3 (4.3%)	
Extra			
None	38 (54.3)	48 (68.6%)	
Nodular density	14 (20.0%)	11 (15.7%)	0.201
Focal asymmetry	18 (25.7%)	11 (15.7%)	
Intramammary lymph nodes			0.13
No	58 (82.9%)	64 (91.4%)	
Yes	12 (17.1%)	6 (8.6%)	
BIRADS-mammography			
1	13 (18.6 %)	35 (50.0%)	**<0.001**
2	35 (50.0%)	31 (44.3%)	
3	22 (31.4%)	4 (5.7%)	
4	-	-	

P value <0.05, statistically significant

Since high breast density is an independent risk factor for breast cancer, we compared patients with low mammographic density (Density A - B, n = 80) and high mammographic density (Density C - D, n = 60). There were no statistically significant differences between the groups except the presence of adenomyosis. While there were 31 (38.8%) patients with adenomyosis in the Density A-B group, there were 39 (65%) patients in the Density C-D group (p = 0.002).

Lastly, we grouped patients according to the BIRADS 1 - 2 and BIRADS 3 - 4 categories. There were 114 patients in the BIRADS 1 - 2 group and 26 in the BIRADS 3 - 4 group. Age ≥ 49.5, gravidity ≥ 3, parity ≥ 2, and the presence of adenomyosis were significantly higher in the BIRADS 3 - 4 category. When the effects of the confounding variables to BIRADS 3 - 4 classifications were sought by logistic regression analysis, the presence of adenomyosis was found to be the sole factor for BIRADS 3 - 4 category [OR 0.19 (95% CI: 0.055-0.636), p = 0.007] (Table 3).

Table 3. Logistic regression analysis of the BIRADS 3-4 group with regard to confounding variables

	Wald	S. E.	P value	Odds Ratio (95% CI)
Age ≥ 49.5	3.158	0.479	0.076	0.43 (0.167- 1.092)
Gravida ≥ 3	0.019	0.563	0.89	1.08 (0.359-3.255)
Parite ≥ 2	2.310	0.624	0.129	0.41 (0.132- 1.292)
Adenomyosis	7.216	0.395	**0.007**	**0.19 (0.055-0.636)**

P value <0.05, statistically significant

4. Discussion

The results of our study suggested that patients with adenomyosis have an increased risk of higher mammographic breast density and BIRADS 3 classification. However, we could not conclude that these mammographic findings will lead to an increased risk of breast cancer in women with adenomyosis.

Breast density is a mammographic finding that is strongly associated with breast cancer risk (11, 12). The fibroglandular tissue appears as white on mammograms as it attenuates X-rays more than fatty tissue (12). Since the majority of breast cancers arise from the glandular and stromal cells, the risk of breast cancer increases with the increase in mammographic breast density. Moreover, underlying cancer may not be visible due to radio-opaque dense tissue. When the extremely dense breasts (Category D) were compared with the almost entirely fatty breasts (Category A), there is a 4.64-fold increase in the risk of breast cancer for the extremely dense breasts (11).

The Breast Imaging Reporting and Data System lexicon has been developed to report mammographic features among radiologists in a standardized manner and for clinicians to standardize their follow-up and management according to the final classification. Women with BIRADS 1 (negative) and 2 (benign findings) categories have the lowest risk of breast cancer (13). On the other hand, BIRADS 3 (probably benign) category is still questionable as it means that the risk of malignancy is lower than 2%; however, it also implies that these probably benign findings should be reassessed within six months (14). According to the results of a recent study with the largest series of BIRADS 3 cases, Berg et al.

reported 1.86% breast cancer over two years, and 57.8% of detected cancers were diagnosed in the first 6 months or earlier, confirming the role of short-range follow-up (15).

The next problem is to explain why the mammographic breast findings of adenomyosis patients are in the higher risk group for breast cancer compared to the control group. Classically both adenomyosis and breast neoplasia are defined as oestrogen-dependent diseases. Indeed, the coexistence of adenomyosis and breast tumour has been shown in many ancient animal studies (16-18). In mice with different breast tumor potentials, it has been shown that all mammary tumour-bearing animals develop uterine adenomyosis (16, 18). High levels of prolactin and growth hormone by pituitary grafting also resulted in both uterine adenomyosis and mammary tumours (17). In addition, tamoxifen use due to chemoprevention of breast cancer is highly associated with uterine adenomyosis in postmenopausal women (19, 20). Eutopic endometrium in adenomyosis shows altered metabolism of steroid sulphatase, aromatase, and 17ß-hydroxysteroid dehydrogenase enzymes leading to local hyperoestrogenism (21-23). In terms of adenomyosis pathophysiology, local hyperoestrogenism plays an active role both in epithelial-mesenchymal transition (24) and hyperperistalsis of the sub endometrial myometrium activating “tissue injury and repair” mechanisms (25). On the other hand, the place of these three main steroidogenic enzymes in breast cancer is indisputable (9, 26, 27). Thus, we can speculate that similar epigenetic, inflammatory, and hormonal pathways might be involved in the pathophysiology of the two lesions. However, the relationship between adenomyosis and cancers has been sought in a couple of studies (28, 29). Although no relationship was found between adenomyosis and breast cancer in both studies, Kok et al. found an increased risk of ovarian, endometrial, and colorectal cancers (28), while Yeh et al. found higher risks of endometrial and thyroid cancers in women with adenomyosis (29).

This study has several limitations to consider. First of all, we could not exclude selection bias due to the retrospective design of the study. Secondly, the radiologic features were noted from the reports of the mammograms, thus the interobserver bias could not be evitable. Lastly, there were a high number of patients excluded due to BIRADS 0 (incomplete evaluation), which might be the reason for not finding a higher classification other than BIRADS 3. On the other hand, we have included patients who have not used any hormonal medications due to adenomyosis or contraception. In addition, since we excluded those with a history of breast biopsy and a personal and family history of malignant breast disease, we only tried to examine the effects of adenomyosis on the breast. Furthermore, all our patients with adenomyosis were histopathologically proven cases.

In conclusion, the results of our study point out the importance of breast screening of women with adenomyosis. We hope that our study will lead to prospective studies that will investigate both the molecular history and clinical consequences of breast diseases in women with adenomyosis.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

None.

Acknowledgments

None to declare.

Authors’ contributions

Concept: N.K., K.K., S.O., Design: N.K., K.K., S.O., Data Collection or Processing: N.K., Y.E.U., Analysis or Interpretation: N.K., H.G., A.Y., Literature Search: N.K., K.K., S.O., Writing: N.K.

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