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Relationship Between Endometriosis, Borderline Adnexal Tumors and Malignant Tumors: A Retrospective Case Study

Endometriozis ile Adneksiyal Borderline ve Malign Tümörler Arasındaki İlişki: Retrospektif Olgu Serisi Çalışması

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ABSTRACT

Aim: The main purpose of this study is to investigate the relationship between ovarian endometriosis and borderline ovarian tumor (BOT) and malignant ovarian tumor.

Materials and Methods: Data were retrospectively collected from patients with BOT or malignant adnexal tumor and endometriosis in the surrounding tissue (in the same piece) in the pathology after gynecological surgery at the tertiary center Obstetrics and Gynecology Clinic, between 2017 and May 2023. Patient age, gravidity, body mass index, family history of cancer, clinical complaints, ultrasound and magnetic resonance imaging (MRI) features of the detected mass, preoperative tumor markers and pathological stages were recorded.

Results: A total of 49 BOTs were diagnosed in this 5.5-year period. 19 of them were serous, 22 of them were mucinous, 7 of them were seromucinous, and 1 of them was endometrioid BOT. In 9 BOT cases, there was pathologically confirmed endometriosis in the same ovary or pelvic tissue remaining in the surgical area. There were 37 malignant epithelial ovarian cancer diagnoses in 5.5 years. Of these, 11 had endometrioid ovarian cancer (1 had endometrioid and clear cell cancer), 25 had serous ovarian cancer and 1 had mucinous ovarian cancer. Endometriosis was associated with 4 cases of serous adenocarcinoma and 4 cases of endometrioid ovarian cancer. Among these patients, BOT patients with endometriosis were younger. Tumor markers were slightly elevated in 3 cases in the BOT group. In women having endometriosis with malignant pathology, preoperative tumor markers were slightly elevated in 3 patients, and tumor markers were normal in the other cases. Infertility was more common in the malignant patient group. MRI findings were more consistent with the pathological diagnosis in the malignant group. All but 1 patient in the malignant group had peroperative frozen pathology and complementary surgery in a single session. Frozen pathology was not performed in all patients in the BOT group, and some patients underwent cystectomy only.

Conclusion: Endometriosis can be associated with malignancies and borderline adnexal tumors with or without endometrioma. We believe that when an adnexal mass is seen in patients who have undergone surgery for the diagnosis of endometriosis, the possibility of malignancy should be considered and per-operative frozen pathology should be performed.

Keywords: Adnexal tumours, borderline ovarian tumour, endometriosis, endometrioma, ovarian cancer

ÖZ

Amaç: Bu çalışmanın temel amacı over endometriozisi ile borderline over tümörü (BOT) ve malign over tümörü arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Veriler, 2017 ve Mayıs 2023 tarihleri arasında üçüncü basamak bir merkezin Kadın Hastalıkları ve Doğum Kliniği'nde jinekolojik cerrahi sonrası patolojide BOT veya malign adneksiyal tümör ve çevre dokuda (aynı piyeste) endometriozis olan hastalardan retrospektif olarak toplandı. Hasta yaşı, gravidite, vücut kitle indeksi, ailede kanser öyküsü, klinik şikayetler, tespit edilen kitlenin ultrason ve manyetik rezonans görüntüleme (MRG) özellikleri, ameliyat öncesi tümör belirteçleri ve patolojik evreler kaydedildi.

Bulgular: Bu 5,5 yıllık dönemde toplam 49 BOT tanısı kondu. Bunların 19'u seröz, 22'si müsinöz, 7'si seromüsinöz ve 1'i endometrioid BOT idi. Dokuz BOT olgusunda aynı overde veya cerrahi alanda kalan pelvik dokuda patolojik olarak doğrulanmış endometriozis vardı. 5,5 yıl içinde 37 malign

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epitelyal over kanseri tanısı konuldu. Bunların 11'inde endometrioid over kanseri (1'inde endometrioid ve berrak hücreli kanser), 25'inde seröz over kanseri ve 1'inde müsinöz over kanseri vardı. Endometriozis 4 seröz adenokarsinom ve 4 endometrioid over kanseri olgusu ile ilişkilendirildi. Bu hastalar arasında endometriozisli BOT hastaları daha gençti. Tümör belirteçleri, BOT grubundaki 3 olguda hafifçe yükselmişti. Malign patolojiye sahip endometriozisli kadınlarda, ameliyat öncesi tümör belirteçleri 3 hastada hafifçe yükselirken, diğer olgularda tümör belirteçleri normaldi. Malign hasta grubunda infertilite daha yaygındı. MRG bulguları malign grupta patolojik tanı ile daha tutarlıydı. Malign gruptaki 1 hasta hariç tüm hastalara peroperatif frozen patoloji ve tek seansta tamamlayıcı cerrahi uygulandı. BOT grubundaki tüm hastalara frozen patoloji yapılmadı ve bazı hastalara sadece kistektomi uygulandı.

Sonuç: Endometriozis, endometrioma olsun ya da olmasın maligniteler ve borderline adneksiyal tümörler ile ilişkili olabilir. Endometriozis tanısı ile cerrahi uygulanan hastalarda adneksiyal kitle görüldüğünde malignite olasılığının göz önünde bulundurulması ve peroperatif frozen patoloji yapılması gerektiğine inanıyoruz.

Anahtar Kelimeler: Adneksiyal tümörler, borderline over tümörleri, endometriozis, endometrioma, ovarian kanser

INTRODUCTION

Endometriosis is an inflammatory disease that affects 10% of women and carries a risk of malignant transformation[1].

Endometriosis is a non-neoplastic pathology with endogenous estrogen production and progesterone-resistant chronic inflammatory features such as tissue invasion, angiogenesis, and reduced apoptosis. These properties may predispose to cancer.

Endometriosis is associated with a 50% increased risk of epithelial ovarian cancer[2,3].

In endometriosis, the total ovarian cancer is increased, especially the endometrioid and clear cell cancer[4]. However, endometrioma excision is not recommended for ovarian cancer prophylaxis. The risk of malignant transformation of endometriosis has been estimated at 1% for premenopausal females and 1% to 2.5% for postmenopausal females[5,6]. Ovarian cancer associated with endometriosis is associated with better overall survival and early stage. Epidemiological studies investigating the relationship between endometriosis and cancer have shown that endometriosis increases the risk of cancer (1.3 to 1.9 times)[7].

Borderline ovarian tumors (BOTs) represent 10-20% of all ovarian epithelial tumors and they are characterized by nuclear atypia and up-regulated cellular proliferation without stromal invasion. They have a low incidence of 4.8/100,000 (Europe) and 1.5-2.5/100,000 (United States) new cases per year, primarily affecting women in their childbearing years. Based on their histologic features, BOTs are classified as serous, mucinous, endometrioid, clear cell, transitional cell, mixed epithelial cell, and Brenner tumors[8]. The same publication has noted that BOTs are more common in endometriosis than ovarian malignancies. In another study, the prevalence of concomitant endometriosis in borderline tumors was reported to be 12%[9].

Our aim in this study is to draw attention to the increase in ovarian malignancies and borderline tumors in women with endometriosis.

MATERIALS AND METHODS

The data of patients who underwent surgery in a tertiary state hospital between May 2017 and January 2023 and were diagnosed with borderline or malignant adnexal tumors in addition to endometriosis in their pathology were screened in accordance with the İstanbul Medipol University Non-invasive Clinical Research Ethics Committee date-decision numbered: 16.03.2023-271 and the Declaration of Helsinki. In the study, a total of 49 BOT and 37 malignant ovarian tumors were operated, and pathologically confirmed endometriosis was detected in nine BOT and eight malignant ovarian tumors. The data obtained from the patients' age, gravida, clinical complaints, ultrasonography and Doppler findings, tumor markers, magnetic resonance imaging (MRI) characteristics, the operation performed, frozen pathology if performed, final pathology, the final state of the patients as a result of hospital and telephone interviews were obtained.

Statistical Analysis

The study is a case series and statistical analysis was not performed.

RESULTS

We screened 49 patients with BOTs and 37 patients with malignant ovarian tumors between May 2017 and January 2023. Nine of the BOT patients had endometriosis, and the median age of these patients was 41 years (2080 years). There were eight endometriosis patients with malignant ovarian tumors, and the mean age of these patients was 52 years (45-76 years) (Tables 1, 2).

The tumour markers were normal in six out of nine patients with a BOT and endometriosis. Tumor markers were normal in five out of eight patients with ovarian malignancy and endometriosis, and did not increase more than twofold in three patients with high tumor markers.

Of 49 patients (19 serous, 22 mucinous, 7 seromucinous, 1 endometrioid borderline tumor) with a pathological diagnosis of BOT, three were serous BOTs (15% of all serous BOTs), and two mucinous BOTs (all mucinous BOTs 9% of patients), three

seromucinous BOTs (40% of all seromucinous BOTs) and one endometrioid BOT were associated with endometriosis.

Of the 37 patients diagnosed with malignant ovarian tumors, one was a mucinous adenocarcinoma, 25 were serous adenocarcinomas (nine lowgrade, 16 highgrade serous adenocarcinomas), 11 were endometrioid-type ovarian carcinomas and one was of mixed type with endometrioid + clear-cell carcinoma cells. Endometriosis accompanied malignant ovarian tumors in eight of the women, three of which were high-grade serous adenocarcinomas (12% of all malignant ovarian serous cancer cases), and five were endometrioid carcinomas (45% of all endometrioid ovarian cancer cases) (Tables 1, 2).

In one high grade serous cancer and one endometrioid cancer, the primary cancer focus was the fimbrial end of the tubal.

In the BOT group, every patient had abdominal pain, cyst detection, and known cyst enlargement. There were no menstrual irregularities and no family histories of cancer. Vaginal bleeding (postmenopausal bleeding) was the most common complaint in malignant cases. In these patients, a cystic mass with solid areas was diagnosed with ultrasound and ovarian cancer was diagnosed with MRI.

The body mass index of the patients in the BOT group was in the normal weight range. Two of the malignant patients were obese.

Four of the malignant patients had a family history of breast and stomach cancer. There was no family history of cancer in the BOT group.

The fertility potential of virgins and young patients in the BOT group was unknown; every patient in the malignant group was married and four were infertile.

In the BOT group, in addition to three patients with known endometrioma, who underwent surgery because the endometrioma grew rapidly during followup, three patients underwent surgery because cysts of unknown origin were diagnosed.

Endometriosis was not mentioned in the preoperative complaints and examinations of patients with malignancy and endometriosis, but preoperative cysts with dense contents were observed in almost all of them.

In both the BOT and malignant groups, a dense cyst, solid area, papillary structure, and a mural nodule were observed on ultrasound, and an intra-cyst enhancing papillary structure or mural nodule was observed on MRI (Tables 1, 2).

Table 1. Characteristics of borderline ovarian tumor cases with endometriosis

No.	Age	Gravida	USG/Doppler	MRI	Tm markers	Operation and time after surgery	Frozen pathology	Final diagnosis
1	20	0	Endometrioma with solid component on the left	Endometrioma with solid component on the left	n	Cystectomy (1 year ago)	Benign ovarian tumor	SMBT (left)
2	23	0	Endometrioma with solid component on the left	Endometrioma with solid component on the left	n	Cystectomy (2.5 years ago)	Borderline tumor	SMBT (left)
3	35	3	Right homogeneous cyst	T1 hypointense-T2 hyperintense cyst	n	1. Cystectomy 2. L/S USO (5 years ago)	None	MBT (right)
4	36	3	Endometrioma with solid component on the right	Endometrioma	n	1. Cystectomy 2. Debulking (1 year ago)	None	SMBT (right)
5	41	5	Homogeneous cyst with bilateral solid areas	Homogeneous cyst	CA 125:47 U/mL	L/S BSO (2021-March)	None	SBT (bilateral)
6	43	0	Endometrioma with solid component on the left-endometrioma on the right	Solid space	n	Debulking (3 years ago)	SBT	SBT (bilateral)
7	43	2	Endometrioma with solid component on the left	Papillary structure	CA 125:56 U/mL	Debulking (4.5 years ago)	Borderline tumor	EBT (left)
8	49	2	Endometrioma on the right	Cyst	CA 125:250 U/mL	TAH+BSO+ omentectomy (1.5 years ago)	Serous cystadenofibroma	MBT (right)
9	80	3	Endometrioma on the left	Endometrioma	n	1. uso 2. tah+uso (2 years ago)	BOT	SBT (left)

SMBT: Seromucinous borderline tumor, SBT: Serous borderline tumour, EBT: Endometrioid borderline tumor, MBT: Mucinous borderline tumor, L/S BSO: Laparoscopic bilateral salpingooopherectomy, L/S USO: Laparoscopic unilateral salpingooopherectomy, MRI: Magnetic resonance imaging, USG: Ultrasonography, Ca: Carcinoma, n: Normal

Table 2. Characteristics of malignant ovarian tumor cases with endometriosis

No.	Age	Gravida	USG/Doppler	Tumor stage	Tm markers	Operation and time after surgery	Frozen	Final diagnosis	CT/RT
1	39	1	Cyst with solid component on the	pT1c2N0Mx	CA 125:87	Debulking (1.5 years ago)	Malignant tumor	HGSC[a] (left tuba)	CT
2	45	1	Bleeding; cancer on the endometrial polyp	PT1a? (tuba) PT3a? (uterus)	CA19-9 2x	TAH+BSO+ right lymphadenectomy (2 years ago)	Endometrium cancer[a]	Endometrium ca+ right tuba endometiroid ca[b]	CT
3	45	1	Cyst with solid component on the left	p T1a N1b Mx (over) p T1b N1a Mx (uterus)	n	Type 3 hysterectomy (3 years ago)	Malignant tumor	Endometrioid over Ca (left side)+ endometrium Ca	CT+RT
4	45	0	Cyst with solid component on the right	pT1aN0Mx	CEA:4	Debulking (2 years ago)	Endometrioid cancer	HGSC[a] (right side)	CT
5	52	0	Concentrated cyst, endometrioma on the left	pT1c1NxMx	n	TAH+BSO (5.5 years ago)	None	Endometrioid (left side)	CT
7	56	4	Cyst with solid component	pT1c1N0Mx	n	Debulking (3 years ago)	Malignant tumor	Endometrioid Ca (right side)	CT
6	58	2	Malignant mass	PT1c2N0Mx (over) PT1aN0Mx (uterus)	n	Debulking (1.5 years ago)	Malignant tumor	Endometrioid over Ca (left side) + endometrium Ca	CT+RT
8	76	0	Cyst with solid component on the right	pT1aN0Mx	n	Debulking (3 years ago)	HGSC[a]	HGSC[a] (right side)	?

[a]Frozen pathology was done for endometrium.

[b]The cancer in the tube has emerged from the endometriosis focus.

HGSC: High grade serous ovarian carcinoma, Ca: Carsinoma, CT: Chemotherapy, RT: Radiotherapy, USG: Ultrasonography

Only cystectomies were performed on two virgin patients in the BOT group. Frozen pathology was performed on six patients and was reported as benign in two patients and BOT in four patients. Peroperative frozen pathology was not performed in three patients, and due to the presence of BOT in the postoperative pathology and keeping in mind their age and fertility expectations, complementary surgery was performed in the second operation, and close observation was performed in one patient. Frozen pathology was performed in seven patients whose final pathology was malignant ovarian tumor, and no frozen pathology was performed in one patient. Patients who were found to be malignant on frozen pathology underwent additional surgery in the same session, and one patient did not have frozen pathology and underwent postoperative chemotherapy (CT) and radiotherapy (RT). CT was given to five of eight malignant patients and CT+RT was given to two patients. Malignant patients with a postoperative period of 1.5 to 5.5 years were contacted by telephone, and every patient was found to be alive and experiencing no recurrence.

None of the patients in the BOT group had peritoneal or distant organ implants, gastrointestinal symptoms or ascites. There were also no recurrences.

DISCUSSION

Endometrioma is a benign condition and malignant transformation is rare (1% in premenopausal women and 1% to 2.5% in postmenopausal women). In the case of large endometriomas (9 cm) and advanced age (>45 years), malignancy should be considered. The mean age of the patients in our malignant patient group was 52 years.

Endometriosis is defined as the presence of endometrial-type mucosa outside the uterine cavity[2].

Endometriosis increases the frequency of clear cell ovarian cancer, endometrioid ovarian cancer and epithelial ovarian cancer[10-12]. Endometriosis is the most common precursor of endometrioid and clear cell carcinoma with a clonal relationship. There is believed to be a relationship between BOTs and endometriosis, explained by molecular and genetic aberrations[13].

Ovarian seromucinous borderline tumors, a rare pathology, are a different tumor group from ovarian epithelioid tumors seen in women of reproductive age. In 2014, the new classification defined these tumors separately, whereas they were previously classified as epithelial ovarian tumors[14]. Finally, the World Health Organization 2020 Classification of Female Genital Tumors recognized seromucinous carcinoma as a separate entity and reclassified it as endometrioid carcinoma with mucinous differentiation[15].

There is information in the literature that the type of endometriosis associated with malignancy is ovarian endometriosis, and that peritoneal or deep endometriosis does not increase the risk of cancer. About one-third of endometrioid and clear cell cancer cases have endometriosis. In fact, endometriosis has been defined as a risk factor or precursor lesion for these cancers. In a ten year follow up, an additional two cases of ovarian cancer are seen for every 1,000 women with ovarian endometriosis[4]. In our study, BOT and endometriosis were found in the pathological specimens of two patients. There was no endometrioma in these patients, and there were no clinical (pain, abnormal vaginal bleeding, etc.) or examination findings (nodule, urethral dilatation, hydrosalpinx, etc.) suggestive of endometriosis. In the group of patients with malignant tumors, an endometrioma was observed in one patient prior to surgery and endometriosis externa was found in the pathological examination of the other patients. As a result of this study, we believe that not only endometrioma but also endometriosis elsewhere should have an impact on the development of malignancy.

CA 125, the most commonly used tumor marker for malignancy in patients, is a tumor marker with low specificity and is already high in women with endometriosis However, it should be considered if the CA 125 test result is >200 U/mL. This is because CA 125 is elevated in 80% of epithelial ovarian tumors[16,17]. However, based on the literature and the data from our study, we found that tumor markers were not useful in the diagnosis of BOTs[18].

BOTs are the tumors with nuclear atypia and up-regulated cellular proliferation, but without stromal invasion. In this way, it is seen less aggressively and at an early age (40s) and the type of treatment should be determined by considering the patient's age and fertility expectation. In our study, the median age in the BOT group was 41 years, which is in line with the literature. Moreover, we performed cystectomy on the patients in the BOT group, who wanted to have a child, and followed them closely. There was no recurrence.

In our patients in whom BOT and ovarian cysts were seen together, we decided to operate because of the most common appearance of solid areas/mural nodules/papillary structures within the cyst. BOT cysts are the cysts with papillary structures in a unilateral cyst, and in an examination, it shows microscopically characteristic broad papillae lined by serous type epithelial cells with abundant eosinophilic cytoplasm admixed with a varying number of endocervical-like mucinous cells[19]. In patients with cysts with malignant pathology, intracyst hyperechogenicity (such as papillary structure or solid area) and Doppler flow in these areas were remarkable on ultrasound.

Seromucinous tumors were associated with endometriosis in 23.1% of the cases and they were bilateral in 30.8%. In the BOT group in our study, two patients had bilateral BOT, three had a lesion on the right, and four had a left lesion. In three of the malignant ovarian tumors detected together with endometriosis, there was ovarian cancer synchronized with endometrial cancer (two in the right ovary, one in the left ovary), two patients had a malignancy originating from the left adnexa and three patients had a malignancy originating from the right adnexa. There were no bilateral malignancies in the malignant patients. In a study examining ovarian cancer data spanning 16 years in 2018, it was reported that 7.3% of ovarian cancer cases were observed in conjunction with endometriosis. Among 35 cases with identified atypical endometriosis in their pathology, BOTs were detected in 11 cases (31%), and the average age of these patients was reported to be 44 years (range: 22-70 years)[9]. Despite the mandatory hiatus imposed by COVID-19 during the five years we scrutinized the data, we identified 8 malignant cases associated with endometriosis. The oldest patient among them was 76 years old, while the average age of the remaining patients was 48 years, aligning with the literature. It should be noted that epithelial ovarian cancer is more common in individuals aged 60 years and above[20].

In ovarian tumors, frozen pathology can diagnose suspicious masses at a high rate (65100%), but the diagnostic value is reduced in borderline tumors and large masses[21]. Peroperative frozen pathology was not used in one patient with malignant pathology in our clinic, and one patient was diagnosed with endometrial cancer synchronized with frozen pathology. The diagnosis of a 3 mm endometrioid type tubal cancer originating from the endometriosis focus at the fimbrial end of the tube in this patient could not be made. This patient was operated on for endometrial cancer and no adnexal mass was found on ultrasound, so the pathology was not alerted for adnexal malignancy.

Malignancy should be considered, especially in adnexal cysts in infertile women. The frequency of infertile patients in the group we studied is remarkable[22].

Endometriosis is not a precancerous disease, but it is not a completely benign disease, either. A malignancy that develops from an endometrioma has similar characteristics to other ovarian tumors. Especially in cases of atypical endometrioma with a solid area and papillary structure, malignancy should

be considered, and then the patient should be referred to MRI. Almost all of our cases with endometrioma in our study had atypical cyst features (solid areas, mural nodules, and increased blood flow in Doppler)[23].

In the presence of abnormal vaginal bleeding in women with endometriosis, we believe that preoperative endometrial sampling is necessary to screen for endometrial pathologies and other genital tumors, aiming to avoid overlooking or missing them (in our study, we had three patients with malignant adnexal tumors).

Study Limitations

In the study, we excluded the results of patients whose specimens were sent to the hospital pathology laboratory from outside centers and patients who underwent surgery in other surgical departments and were found to have additional malignancy/borderline tumors in addition to endometriosis.

CONCLUSION

Currently, surgical treatment is avoided for the treatment of endometriosis/endometrioma. However, based on our study results and the literature, we believe that ultrasound, Doppler and MRI should be used more freely in endometriosis patients. We also recommend that if there is clinical or radiologic suspicion of malignancy, the patient should be informed about the surgical treatment option and frozen pathology should be performed intraoperatively in those who undergo surgery.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Medipol University Non-invasive Clinical Research Ethics Committee date-decision numbered: 16.03.2023-271.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.K.A., N.H., Concept: C.C., N.H., Design: C.C., N.H., Data Collection or Processing: Ö.K.A., Analysis or Interpretation: Ö.K.A., N.H., Literature Search: Ö.K.A., C.C., Writing: C.C.

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