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ENDOMETRIAL NEOPLASIA WITH ADJUVANT TAMOXIFEN TREATMENT IN BREAST CANCER PATIENTS : REPORT OF NON-ENDOMETRIOID SUBTYPES

ADJUVAN TAMOKSİFEN TEDAVİSİ ALAN MEME KANSERLİ HASTALARDA ENDOMETRİAL NEOPLAZİ : NON-ENDOMETRİOİD ALT GRUPLARININ SUNUMU

[1]Yıldız ERHAN [1]Osman ZEKİOĞLU [2]Mustafa COŞAN TEREK [2]Levent AKMAN

[2]Aydın ÖZSARAN [1]Yılmaz DİKMEN [2]Fatih ŞENDAĞ

[1]Department of Pathology Ege University Faculty of Medicine, Turkey

[2]Department of Obstetrics and Gynecology Ege University Faculty of Medicine, Turkey

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Anahtar kelimeler : Tamoksifen, endometrial neoplazi, meme kanseri, transvajinal sonografi

SUMMARY

The aim of the present study is to report the clinicopathologic features of endometrial cancers subsequently develepod after adjuvant treatment of breast cancer with tamoxifen. Seven endometrial cancers in tamoxifen-treated breast cancer patients were treated at our institution between 1994 and 2002. Medical reports of the patients were evaluated retrospectively. All patients were postmenopausal and one patient was nulliparous.

The age at discovery of the endometrial carcinoma ranged from 53-78. The menopausal age ranged from 40-53. Six of seven postmenopausal patients had postmenopausal uterine bleeding as the initial complaint. Only one patient was found to have endometrial cancer at annual gynecologic examination. Endometrial neoplasia was diagnosed by dilatation and curettage in all cases. The patients had been treated with 20 mg of tamoxifen daily for 1-14 years. Six patients were found to have endometrial carcinoma during adjuvant tamoxifen treatment. Only one patient developed endometrial carcinoma six years after the cessation of adjuvant tamoxifen treatment. Histopathologic examination of the specimens revelaed five cases of adenocarcinoma and two cases of sarcoma. Malignant mixed mesodermal tumor and adenosarcoma of the endometrium developed in long-term tamoxifen users (8 and 14 years, respectively).

Patients with breast cancer using adjuvant tamoxifen treatment, especially the long-term users should be monitored for the possibility of endometrial neoplasia. It is notable that five out of seven endometrial malignancies were not of endometrioid subtype.

ÖZET

Bu çalışmanın amacı, meme kanserli hastalarda adjuvan tamoksifen tedavisi sonrasında gelişen endometrial kanserin klinik ve patolojik özelliklerini sunmaktır. Kliniğimizde; 1994 ve 2002 yılları arasında, meme kanseri nedeniyle tamoksifen kullanımı sonrasında endometrial kanser tanısı ile tedavi edilen yedi hastayı inceledik. Hastaların tıbbi bilgilerini retrospektif olarak değerlendirdik. Bütün hastalar postmenapozal dönemdeydi ve bir hasta nullipardı.

Endometrial kanser, hastalarda 53-78 yaş arasında ortaya çıkmıştır. Hastaların menapoz yaşları 40-53 yaş arasındadır. Yedi postmenapozal hastanın altısında, ilk şikayet postmenapozal uterin kanamadır. Sadece bir hastada endometrial kanser yıllık jinekolojik muayane sırasında saptanmıştır. Tüm hastalarda endometrial kanser tanısı dilatasyon ve küretaj ile konmuştur. Hastalar 1-14 yıl arasında, günlük 20 mg tamoksifen ile tedavi edilmiştir. Altı hastada, adjuvan tamoksifen tedavisi sırasında endometrial kanser saptanmıştır.

Yazışma adresi: Mustafa COŞAN TEREK, Department of Obstetrics and Gynecology Ege University Faculty of Medicine Bornova, Izmir 35100 Turkey

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Sadece bir hastada, adjuvan tamoksifen tedavisi kesildikten altı yıl sonra endometrial kanser gelişmiştir. Örneklerin histolojik değerlendirilmesinde, beş hastada adenokarsinom ve iki hastada sarkom saptanmıştır. Endometriumun malign mikst mezodermal tümör ve adenosarkomu uzun dönem tamoksifen kullananlarda gelişmiştir (8 ve 14 yılda gözlendi).

Adjuvan tamoksifen tedavisi kullanan meme kanserli hastalar, özellikle uzun süre kullananlar, endometrial kanser olasılığı açısından izlenmelidir. Yedi endometrial malignitenin, ikisinin non-endometrioid altgrubunda olması dikkate alınmalıdır.

INTRODUCTION

Tamoxifen is used for adjuvant therapy of early and metastatic breast cancer both providing improvement in disease-free survival and reducing the risk of developing cancer in the contralateral breast [(1)]. Tamoxifen belongs to a group of drugs termed selective estrogen receptor modulators that are tissue specific in their actions. Tamoxifen affects a variety of organ systems other than the breast. One of the most important side effects of tamoxifen appears to be its proliferative effect on the endometrium, which may result in the development of polyps and malignant neoplasms[(2)]. Tamoxifen users have a two-fold to seven-fold increased risk of endometrial cancer and the risk seems to be highest after long-term use 3-4.

The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. National Surgical Adjuvant Breast and Bowel Project P-1 study was done to test this hypothesis[(5)]. Women (n=13,388) were randomized to receive placebo or 20 mg/day tamoxifen for five years. Tamoxifen reduced the risk of invasive breast cancer by 49% after a median follow-up of 55 months. The rate of endometrial cancer was found to be increased in the tamoxifen group (risk ratio=2.53). This increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I and no endometrial cancer deaths have occurred in this group5. However, the use of using tamoxifen as a preventive agent against breast cancer in healthy women is a controversial issue.

The aim of this study is to determine the clinicopathologic features of endometrial cancers subsequently develepod in breast cancer patients during or after adjuvant tamoxifen treatment in a single institution.

PATIENTS AND METHODS

Between 1994 and 2002, seven endometrial carcinomas were found in tamoxifen-treated breast cancer patients, who subsequently underwent abdominal hysterectomy and bilateral salpingooophorectomy followed by adjuvant radiotherapy at the Ege University Hospital. Pelvic and paraaortic lympadenectomy was not performed. Figure 1 and 2 demonstrates the adenosarcoma developed in case number 4. The clinical characteristics of seven tamoxifen treated breast cancer patients with endometrial carcinomas are summarized in Table 1.

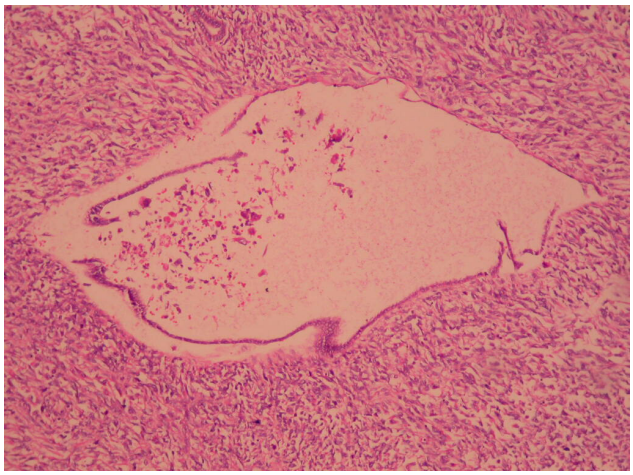

Figure 1. Endometrial adenosarcoma after 14 years of tamoxifen treatment in a 67-year-old breast cancer patient. Low-power view of periglandular cuffing which is diagnostic of adenosarcoma (Hematoxylin and Eosin)

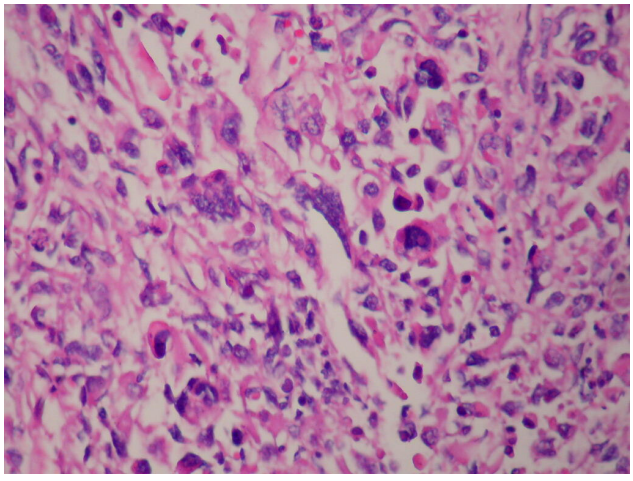

Figure 2. Endometrial adenosarcoma after 14 years of tamoxifen treatment in a 67-year-old breast cancer patient. High-power view of cellular atypia of stromal cells (Hematoxylin and Eosin)

Histopathologic examination of the specimens revelaed five cases of adenocarcinoma and two cases of sarcoma. Malignant mixed mesodermal tumor and adenosarcoma of the endometrium developed in long-term tamoxifen users (8 and 14 years, respectively). Malignant mixed mesodermal tumor and adenosarcoma were homologous in type. Five out of seven endometrial malignancies were not of endometrioid subtype.

The age at discovery of the endometrial carcinoma ranged from 53-78. All patients were postmenopausal. The

menopausal age ranged from 40-53. Six of seven postmenopausal patients had postmenopausal uterine bleeding. Only the patient number five was found to have endometrial cancer at annual gynecologic examination. The patients had been treated with 20 mg of tamoxifen daily for 1-14 years. Six patients were found to have endometrial carcinoma during adjuvant tamoxifen treatment. Only the patient number three developed endometrial carcinoma 6 years after the cessation of adjuvant tamoxifen treatment. Transvaginal sonographic and histopathologic findings were summarized in Table 2.

Patient No : 6 demonstrated recurrent tumor at the vaginal apex two years after the initial diagnosis of endometrioid adenocarcinoma grade 2 limited to the endometrium.

Table 1. Clinical aspects of endometrial carcinoma in tamoxifen-treated breast cancer patients

Patient no.	age	Menopausal age	Systemic Disease	Parity	Abortus	Age at breast cancer diagnosis (in years)	Duration of tamoxifen treatment (in years)
1	68	53	HT	6	0	68	1
2	61	45	DM	2	1	51	10
3	78	40	HT	6	0	64	8
4	67	50	HT, DM	4	1	53	14
5	53	43	HT, DM	0	0	51	2
6	57	50	DM	3	3	53	4
7	66	51	HT	4	0	65	1

HT: Hypertension, DM: Diabetes mellitus

Table 2. The sonographic and histopathologic features of endometrial carcinomas in tamoxifen-treated breast cancer patients

Patient no	Transvaginal sonography	Grade	Myometrial invasion	Breast cancer histology	Histologic type
1	-	3	½ inner	IDC	Serous papillary
2	Endometrial thickness 7 mm, heterogenous endometrial stripe	3	½ inner	IDC	Clear cell
3	Uterus 12 x 7.5 in diameter with irregular borders	3	1/1	IDC	Malignant mix Mullerian tumor
4	Intrauterine heteroechogenic mass 4.7 x 3 cm in diameter	3	1/1	IDC	Adenosarcoma
5	Endometrial thickness 18 mm	2	½ inner	IDC	Endometrioid
6	Endometrial thickness 6 mm	2	Limited to endometrium	IDC	Endometrioid
7	Endometrial thickness 25 mm	2	½ inner	IDC	Endometrioid and mucinous

IDC: Invasive ductal carcinoma

DISCUSSION

There are limited data on the histologic characteristics of endometrial cancers occuring after tamoxifen treatment. Magriples et al[6] reported that 67% of the endometrial cancers that developed in 15 tamoxifen-treated breast cancer patients were high grade or of unfavorable histologic subtypes, compared with 24% of those that developed in 38 breast cancer patients who had not received tamoxifen.

Cohen et al[7] presented a clinicopathologic comparison of women on tamoxifen who developed endometrial cancer (n=12) and those on tamoxifen who did not develop cancer (n=261). Tamoxifen-treated breast cancer patients

who developed endometrial cancer are significantly older, more often have postmenopausal bleeding, have had a longer interval since the diagnosis of breast cancer, and

have received chemotherapy less often than those who did not develop endometrial cancer. Only eight (66.7%) had postmenopausal bleeding, and a preoperative diagnosis of endometrial cancer was made in only six (50%). When considering postmenopausal bleeding as a marker for endometrial cancer in the study patients, sensitivity was 67% and specifity was 98%. In the present study, all the patients demonstrated postmenopausal uterine bleeding except one. Only one patient was found to have endometrial cancer at annual gynecologic examination. Endometrial neoplasia was diagnosed by dilatation and curettage in all cases.

Silva et al[8] showed that 10 (77%) of 13 postmenopausal patients who developed endometrial carcinoma after tamoxifen treatment had endometrial polyps, whereas 16 (34%) of 47 patients in a comparable group who did not receive tamoxifen had endometrial polyps. Deligdisch et al[9] reported that 15 of 33 endometrial carcinomas that developed in postmenopausal breast cancer patients subsequent to adjuvant tamoxifen treatment were found in endometrial polyps. It is, however, not clear, as Deligdisch et al[9] had addressed, whether the relatively high number

of non-endometrioid carcinomas is related to the tamoxifen therapy or to other factors, such as the advanced age of the patients or to both.

The effect of tamoxifen as a potent antiestrogenic agent is well established in the adjuvant therapy of breast cancer. If the effect of tamoxifen on the endometrium is that of an estrogen agonist, associated endometrial carcinomas could be expected to have prognostic characteristics similar to those associated with unopposed estrogen use. This issue was addressed by Nishimura et al[10] and they refuted this theory by their case series report. In their series eight of 10 tumors showed myometrial invasion and two tumors showed lymph node metastasis[10].

In the present study, all patients were postmenopausal and one patient was nulliparous. The age at discovery of the endometrial carcinoma ranged from 53-78. The menopausal age ranged from 40-53. The patients had been treated with 20 mg of tamoxifen daily for 1-14 years. Five patients were found to have endometrial carcinoma during adjuvant tamoxifen treatment. Only one patient developed endometrial carcinoma 6 years after the cessation of adjuvant tamoxifen treatment. Histopathologic examination of the specimens revelaed four cases of adenocarcinoma and two cases of sarcoma. Five out of seven patients were not of endometrioid subtype.

Little is known about steroid receptor status, somatic alterations in oncogenes and tumor suppressor genes, and inherited susceptibility in endometrial carcinomas associated with tamoxifen use. Esteller et al[11]. presented a 79-year-old breast cancer patient who received adjuvant tamoxifen treatment (20 mg per day for 5 years) and subsequently developed endometrial carcinoma. The endometrial carcinoma was negative for estrogen receptors and weakly positive for progesterone receptors. In addition, analysis of K-ras, c-erbB2/neu, cyclin D1, and p53 status revealed a codon 12 point mutation in the K-ras oncogene. The patient was determined not to be a carrier of germ-line mutations in cytochrome P-450 1A1 (CY1A1), an estrogen-metabolizing gene previously associated with enhanced endometrial cancer risk, but she was a carrier of a methylenetetrahydrofolate reductase gene variant related with putative alterations in DNA methylation.

Kazandi et al[12] investigated the frequency of ovarian cysts in tamoxifen-treated postmenopausal breast cancer patients along with endometrial thickening detected by transvaginal sonography. During the study period five of 38 tamoxifen-treated postmenopausal patients (13.2%) had ovarian cysts. The mean tamoxifen treatment interval of the patients with an ovarian cyst was 22.4 ± 18.4 months. Three patients with ovarian cysts underwent laparatomy revealing simple cysts on histopathological examination.

The development of endometrial malignant mixed Mullerian tumors may be linked to long-term tamoxifen use[13]. Bergman et al[14] conducted a case-control study on the risk and prognosis of endometrial cancer after tamoxifen use in Netherlands. Endometrial cancers of stage III and IV occurred more frequently in long-term tamoxifen users (≥ 2 years) than in non-users. And also, 3-year endometrial-cancer-specific survival was significantly worse for long-term tamoxifen users. They reported 8 cases of malingnant mixed Mullerian tumors and sarcomas in 54 breast cancers using tamoxifen ≥ 2 years. In the present study, malignant mixed Mullerian tumor and adenosarcoma of the endometrium developed in long-term tamoxifen users (8 and 14 years, respectively). Two cases developed endometrial cancer after one year of tamoxifen treatment.

In a recent report of Chen et al[15] endometrial cancers occurred at 36 months, 28 months, and 33 months after initial treatment for the breast cancers in three premenopausal women aged 46, 43, and 39, respectively. The patients became menopausal after six courses of chemotherapy ranging from three months to 14 months. Only one patient complained of vaginal spotting before diagnosis and the other two patients only complained of increasing purulent vaginal discharge. All patients received standard treatment for endometrial cancer and none of them died of their disease but one patient died of recurrent breast cancer 52 months later. This report points out to the estrogenic action of tamoxifen in a low-estrogen environment and possible risk of developing endometrial malignancy. In a chemoprevention trial, endometrial carcinoma has been reported in women who were premenopausal at the start of tamoxifen and who became amenorrheic during long-term tamoxifen treatment with proved low serum estrogen levels. Sonography of the endometrium in those women on tamoxifen showed an increased endometrial thickness[16].

In the follow-up of breast cancer patients on tamoxifen therapy, a yearly gynecologic examination together with a cervical cytological sampling is enough for screening. However, in case of endometrial cancer risk factors or cervical stenosis a yearly transvaginal sonographic surveillance shov ld be recommended[17].

In conclusion, patients with breast cancer using adjuvant tamoxifen treatment should be monitored for the possibility of endometrial neoplasia. The presence of non-endometrioid subtypes (5/7) is notable in the present case series report.

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