CASE REPORT

Ovarian Tumors in 6 Patients Using Tamoxifen for Breast Cancer

Jale **METİNDİR**[1], Gülay **BİLİR**[2]

[1]*Ankara Oncology Training and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey*
[2]*Ankara Oncology Training and Research Hospital, Department of Pathology, Ankara, Turkey*

Received 02 August 2005; received in revised form 03 July 2006; accepted 05 July 2006

Abstract

Tamoxifen is a synthetic, nonsteroidal, antiestrogenic drug that is widely used for the therapy of early and metastatic breast cancer patients positive for estrogen receptor proteins. Despite the availability of extensive data on various endometrial pathologies caused by exposure to tamoxifen, there are only a few sporadic cases of malignant and benign ovarian tumors thus far reported, which havedeveloped coincidentally with tamoxifen treatment.

A retrospective review on 164 premenopausal and postmenopausal women treated with tamoxifen for breast cancer and followed up by the gynecology outpatient clinic at Ankara Oncology Training and Research Hospital between January 1996 and December 2004 was carried out. Of these, a group of patients who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for ovarian pathologies, after tamoxifen treatment for breast cancer, were examined. In this report, we present six cases of ovarian tumors diagnosed when using tamoxifen for breast cancer. We have discussed the development of ovarian tumors in patients using tamoxifen for breast cancer.

Keywords: breast cancer, tamoxifen, ovarian tumor

Özet

Tamoksifen Kullanan Meme Kanserli Hastalarda Görülen 6 Over Tümörü Vakası

Tamoksifen, pozitif östrojen reseptör proteini olan erken ve metastatik meme kanseri hastalarında yaygın olarak kullanılan sentetik, non-steroid, antiöstrojen bir ilaçtır. Tamoksifen kullanımına bağlı değişik endometriyal patolojilere ait geniş veriler bulunmasına rağmen, raporlanmış malign ve benign over tümörü vakaları birkaç sporadik vaka şeklindedir.

Ankara Onkoloji Eğitim ve Araştırma Hastanesi Kadın Hastalıkları Polikliniği'ne Ocak 1996-Aralık 2004 yılları arasında başvuran 164 pre ve postmenopozal tamoksifen kullanan meme kanserli kadın retrospektif olarak taranmıştır. Tamoksifen tedavisi sırasında teşhis edilen over patolojisi nedeniyle, total abdominal histerektomi ve salpingo-ooforektomi yapılan meme kanserli hastalar incelenmiştir. Bu çalışmada, pre ve postmenopozal meme kanserli tamoksifen kullanan ve over tümörü saptanmış 6 vaka sunulmuştur. Aynı zamanda, tamoksifen kullanan meme kanserli hastalarda over tümör gelişimi tartışılmıştır.

Anahtar sözcükler: meme kanseri, tamoksifen, over tümörü

Introduction

Tamoxifen is a synthetic, nonsteroidal, antiestrogenic drug that is widely used for the therapy of early and metastatic breast cancer patients positive for estrogen receptor proteins (1). Treatment options of tamoxifen are related primarily to its antiestrogenic properties, although the drug may also act by non-estrogen receptor related mechanisms of action. The response of estrogen-sensitive tissues to tamoxifen varies among different species and sites of action (2,3). This tissue specific action brings about the paradox of tamoxifen as an anticancer drug in breast cancer and as a carcinogenic agent in the endometrium (4), and contraindicative on the female genital tract as a whole (5). The effect of tamoxifen on human ovaries was described by Klopper and Hall (6). Tamoxifen was shown to induce ovulation in anovulatory infertile women instead of working as a contraceptive. Tamoxifen induces estrogen production in the premenopausal ovary, while follicle stimulating hormone (FSH) and luteinizing hormone (LH) do not rise or do so only slightly. This may indicate that tamoxifen has a direct effect on the ovaries of premenopausal women or at least an effect that is not through the classical route of the hypothalamic-pituatary-ovarian axis (2). Very little is known about the effects of tamoxifen on the ovary.

Corresponding Author: Dr. Jale Metindir
Ahmet Mithat Efendi Sok. 58/11
Çankaya 06550 Ankara, Türkiye
Phone : +90 312 336 09 09/5224
GSM : +90 532 562 23 99
E-mail : jmetindir@ttnet.net.tr

Several reports suggest that there may be an association betweeen tamoxifen exposure and development of ovarian cyst and/or endometriosis (7-10). It has also been suggested that tamoxifen may increase the risk of ovarian cancer in premenopausal women (11). Tamoxifen or its metobolite 4-OH-tamoxifen have a direct antiproliferative effect on human ovarian carcinoma specimens (12). Long-term treatment with 4-OH -tamoxifen is able to diminish both the antiproliferative and apoptotic action of tamoxifen on BG-1 (LT) ovarian cancer cells (12). Tamoxifen has been reported to induce DNA adducts which have mutagenic potential in the endometrium (13). Further study of the direct mutagenic effect of tamoxifen on DNA is warranted.

However, the precise mechanism underlying the effects of tamoxifen in ovarian tumor is not completely understood. There are only sporadic cases of ovarian tumors thus far reported, which have developed coincidentally to tamoxifen treatment (10,14). Here below, we describe, 6 pre- and postmenopausal breast cancer cases treated with tamoxifen and diagnosed with ovarian tumors.

Case Report

We have carried out a retrospective review of tamoxifen-treated 164 premenopausal and postmenopausal women with breast cancer who were followed up at the outpatient clinic of Ankara Oncology Training and Research Hospital between January 1996 and December 2004. We examined a selected group of breast cancer patients who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for ovarian pathologies after the diagnosis of breast cancer and treatment with tamoxifen. These cases were referred for routine gynecologic examination during tamoxifen treatment to Department of Gynecology from Departments of Surgery at Ankara Oncology Training and Research Hospital.

All patients were treated with primary surgery for breast cancer. After surgical procedure, they were treated with tamoxifen and chemotherapy [six cycles of standart dose FEC (5-fluorouracil, epirubicin and cyclophosphamide) or FAC (5-fluorouracil, adriamycin and cyclophosphamid) or CMF (cyclophosphamid, methotrexate and 5-fluorouracil) or AC (adriamycin, cyclophosphamide)] and radiotherapy. Tamoxifen was administered orally 10 mg twice a day. Modified radical mastectomy was the primary treatment in 6 patients. All patients who received tamoxifen were assessed clinically by gynecological examination and by transvaginal ultrasonography twice a year.

Case 1. A 63-year-old multiparous women presented with routine gynecologic examination during tamoxifen treatment. She had a history of left modified radical mastectomy for invasive ductal carcinoma of the breast. After surgical procedure, she was treated with six cycles of standart dose FAC. She had been taking tamoxifen citrate 20 mg/day for 35 months. Pelvic examination revealed a left adnexal mass. Serum level of CA 125 was elevated (94.9 IU/ml). Transvaginal ultrasonography showed 50x45x45 mm in diameter cyst with papillary projection on left ovary. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy was performed. The postoperative histological diagnosis was serous cystadenocarcinoma.

Case 2. A 41-year-old multiparous women presented with routine gynecological examination during tamoxifen treatment. She had a history of left modified radical mastectomy for node-positive invasive ductal carcinoma of the breast. After surgical procedure, she was treated with six cycles of standart dose FEC and radiotherapy. She had been taking tamoxifen citrate 20 mg/day for 3 months. Pelvic examination revealed a right adnexal mass. Serum level of CA 125 was not elevated (20 IU/ml). Transvaginal ultrasonography showed 104x52 mm in diameter solid tumor on right ovary. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The postoperative histological diagnosis was stromal edema and cortical fibrotechal hyperplazia.

Case 3. A 52-year-old multiparous women presented with routine gynecological examination during tamoxifen treatment. She had a history of left modified radical mastectomy for invasive ductal carcinoma of the breast. After surgical procedure, she was treated with six cycles of standart dose FAC. She had been taking tamoxifen citrate 20 mg/day for 4 months. Pelvic examination revealed a right adnexal mass. Serum level of CA 125 was elevated (364 IU/ml). Transvaginal ultrasonography showed 55x44 mm in diameter cyst with papillary projection on right ovary. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy was performed. The postoperative histological diagnosis was serous cystadenocarcinoma.

Case 4. A 36-year-old multiparous women presented with irregular bleeding during tamoxifen treatment. She had a history of left modified radical mastectomy for node-positive invasive ductal carcinoma of the breast. After surgical procedure, she was treated with six cycles of standart dose CMF and radiotherapy. She had been taking tamoxifen citrate 20 mg/day for 48 months. Pelvic examination revealed a right adnexal mass. Dilatation and curratage was performed and histology result showed active proliferative endometrium. Serum level of CA 125 was not elevated (16.3 IU/ml). Transvaginal ultrasonography showed 40x50x30 mm in diameter solid tumor on right ovary. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The postoperative histological diagnosis was ovarian leiomyoma.

Case 5. A 52-year-old multiparous women presented with abdominal mass. She had a history of left modified radical mastectomy for node-positive invasive ductal carcinoma of the breast. After surgical procedure, she was treated with six cycles of standart dose CMF and radiotherapy. She had been taking tamoxifen citrate 20 mg/day for 8 months. Pelvic examination revealed a right giant adnexal mass. Serum level of CA 125 was not elevated (24 IU/ml). Transvaginal ultrasonography showed 250x200 mm in diameter solid tumor on right ovary. Total abdominal hysterectomy and bilateral

salpingo-oophorectomy was performed. The postoperative histological diagnosis was ovarian leiomyoma.

Case 6. A 46-year-old multiparous women presented with routine gynecological examination during tamoxifen treatment. She had a history of left modified radical mastectomy for node-positive invasive ductal carcinoma of the breast. After surgical procedure, she was treated with eight cycles of standart dose. She had been taking tamoxifen citrate 20 mg/day for 3 months. Pelvic examination revealed a left adnexal mass. Serum level of CA 125 was not elevated (20 IU/ml). Transvaginal ultrasonography showed 35x30 mm in diameter solid tumor on left ovary. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The postoperative histological diagnosis was endometriosis.

In these 6 women, the mean age was 48.33±9.52 (range: 36-63) years. The mean interval between breast cancer and ovarian tumor was 27.66±17.18 (range: 9-52) months. Mean duration of tamoxifen treatment until surgery was 22.16±19.46 (range: 3-48) months.

Discussion

In our study, two cases of ovarian cancer were identified. Tamoxifen is structurally similar to clomiphene citrate, a drug used to stimulate ovulation in women trying to conceive. Since it is known that epithelial ovarian cancer risk may be increased by factors that increase ovulation, this effect of tamoxifen on the premenopausal ovary may result in an increase in ovarian cancer risk (11). A model for ovarian epithelial malignancy has been proposed for the pathogenesis of cystadenoma or cystadenocarcinoma of the ovaries in humans, based as a consequence of either direct gonadotrophic or estrogenic stimulation (15). Despite this theoretical concern, only anecdotal reports of ovarian cancer have been reported in tamoxifen treated patients (14,16).

In one study, no increase in risk of ovarian cancer in tamoxifen-exposed patients among over 2700 women (RR: 0.7) was reported (17). Similarly, only two cases of ovarian cancer were identified among 1419 tamoxifen-treated women compared with 3 cases in 1424 women receiving placebo in another prospective adjuvant breast cancer trial (18). In a population-based, nested case-control study, the risk of second primary ovarian cancer was investigated among breast cancer patients receiving tamoxifen. The matched odds ratio for ovarian cancer was 0.6, but was not statistically significant (19).

In the study by McGonicle et al. (20), where no patient exposed to tamoxifen was found to have ovarian cancer compared with nearly 10% of those who did not receive tamoxifen, are consistent with prior reports that failed to find an increase in ovarian cancer risk as a result of tamoxifen exposure.

Another possible etiologic factor contributing to the occurence of ovarian tumors may be due to the fact that endometrial and ovarian carcinomas share certain common genetic risk factors, and women with breast malignancy are more likely to develop endometrial or ovarian cancer, regardless of treatment with tamoxifen (21).

On the other hand, it is possible that tamoxifen actually protects against the development of ovarian cancer. Tamoxifen is known to decrease gonadotropin levels in postmenopausal women (22). It has been suggested that elevated gonadotropins may increase ovarian cancer risk (23). Shiffenbauer et al. (24) demonstrated that an increase in gonadotropins after ovariectomy is associated with increased angiogenesis of ovarian cancer spheroids in a mouse model. Because angiogenesis is important in the process of carcinogenesis, a reduction in gonadotropins over normal postmenopausal levels offers a possible mechanism by which tamoxifen may decrease ovarian cancer risk (25).

Since estrogen receptor (ER) is present in about 60% of ovarian cancer cases, and tamoxifen has been shown to have a beneficial effect on cisplatin-refractory ovarian cancer, it is important to examine the results of a long-term treatment of ovarian cancer cells with tamoxifen. Zhou et al. (12) demonstrated that long-term treatment with 4-OH-tamoxifen is able to diminish both the antiproliferative and apoptotic action of tamoxifen on BG-1 ovarian cancer cells.

Table 1. Clinical and pathologic features of tamoxifen-treated breast cancer patients who subsequently developed ovarian tumors

Age*	Interval** (months)	Length of tamoxifen (months)	TVU (Preoperative)	Ovarian tumor histopathology
63	41	35	LO: 50X45X45 mm cyst with papillary projection	LO: Serous cystadenocarcinoma
41	9	3	RO: 104X52 mm solid tumor	RO: Cortical fibrotechal hyperplasia
52	13	4	RO: 55x44 mm cyst with papillary projection	RO: Serous cystadenocarcinoma
36	52	48	RO: 40x50 mm solid tumor	RO: Ovarian leiomyoma
52	12	8	RO: 250x200 mm solid tumor	RO: Ovarian leiomyoma
46	39	35	LO: 35x30 mm cyst	LO: Endometriosis

*Age at the diagnosis of breast cancer
**Interval between breast cancer and ovarian tumor

We described one case of ovarian endometriosis in tamoxifen treated breast cancer patients. Her menstruation maintained, and duration of tamoxifen use was 35 months. Anecdotal reports have suggested that tamoxifen may increase the occurence of endometriosis or cause progression of preexisting endometriosis (7-9). Endometriosis occurs almost exclusively in women of reproductive age. However in postmenopausal patients taking tamoxifen, adenomyosis and endometriosis have both been reported (10).

Mc Cluggage et al. reported a spectrum of neoplastic change, from benign adenofibroma, to borderline, to endometrioid adenocarcinoma, within an ovarian cyst, suggesting that tamoxifen might cause proliferative and in rare case instances malignanat change in endometriosis (26). The mechanism of tamoxifen-induced malignant transformation is still unknown, and local estrogenic stimulation by tamoxifen has been widely proposed as the main candidate (26). Okugawa et al. (27) presented a case of ovarian endometrioid adenocarcinoma which arose from an endometriotic cyst in a postmenopausal woman under tamoxifen therapy for breast cancer.

We described two cases of ovarian leiomyoma in tamoxifen treated breast cancer patients. Leiomyoma is a distincly unusual tumor of the ovary. In contrast to the uterus and supporting ligaments where smooth muscle is relatively abundant the ovary itself is devoid of smooth muscle (28). Histogenically, several theories have been offered to explain the origin of ovarian leiomyoma. Kleitsman (29) suggested that the undifferentiated germ cell in the ovarian stroma may be stimulated to differentiate into smooth muscle, with eventual leiomyoma formation. Wellman (30) proposed that the origin of these tumors may be areas of ovarian endometriosis that contain smooth muscle cells. The consensus of most recent reports is that primary ovarian leiomyomas originate from the walls of blood vessels in the ovarian hilus or from the smooth muscle fibers near the attachment of the ovarian ligament (31,32). Ovarian leiomyoma is often described together with uterine leiomyoma, suggesting an identical hormonal stimulant. Our cases support, estrogenic activity on ovary of tamoxifen and hypothesis of a hormonal stimulus effecting ovarian leiomyoma.

We described a patient with cortical fibrothecal hyperplasia in this study. We demostrated that the possible effect of tamoxifen in the growth of stromal edema and cortical fibrothecal hyperplasia which occured after three months of tamoxifen therapy.

In this report, we discussed the development of ovarian tumors in patients using tamoxifen for breast cancer. Further studies are necessary to better define any association between tamoxifen and ovarian tumors.

References

1. Early Breast Cancer Trialists' Collaborative Group Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. Lancet 1992;339:1-15.
2. Wolf DM, Fuqua SAW. Mechanism of action of antiestrogens. Cancer Treatm Rew 1995;121:247-71.
3. Pink JJ, Jordan VC. Models of estrogen receptor regulation by estrogen and antiestrogens in breast cancer cell lines. Cancer Res 1996;56:2321-30.
4. Fornander T, Cedermark B, Mattson A et al. Adjuvant tamoxifen in early breast cancer: occurence of new primary cancers. Lancet 1989;i:117-20.
5. Mourits MJE, De Vries EGE, Willemse PHB et al. Tamoxifen treatment and gynecologic side effects: A review. Obstet Gynecol 2001;97:855-66.
6. Klopper A, Hall M. New synthetic agent for induction of ovulation: Preliminary trial in women. BMJ 1971;2:152-4.
7. Hajjar LR, Kim W, Nolan GH et al. Intestinal and pelvic endometriosis presenting as a tumor and associated with tamoxifen therapy: a report of a case. Obstet Gynecol 1993;82:642-4.
8. Buckley CH. Tamoxifen and endometriosis Case report. Br J Obstet Gynecol 1990;97:645-6.
9. Ford MRW, Turner MJ, Wood C, Soutter WP. Endometriosis developing during tamoxifen therapy. Am J Obstet Gynecol 1988;158;1119-20.
10. Cohen I, Altaras MM, Lew S et al. Ovarian endometrioid carcinoma and endometriosis developing in postmenopausal breast cancer patient during tamoxifen therapy: A case report and review of the literature. Gynecol Oncol 1994;55:443-7.
11. Spicer DV, Pike MC, Henderson BE. Ovarian cancer and long-term tamoxifen in premenopausal women. Lancet 1991;337:1414.
12. Zhou R, Treeck O, Horn F, Ortmann O. Effects of prolonged tamoxifen on receptor expression and apoptosis of ovarian cancer cells. Gynecol Oncol 2005;96:678-83.
13. Terashima I, Suzuki N, Shibutani S. Mutagenic potantial of alpha-(N2-deoxyguanosinyl) tamoxifen lesions, the major DNA adducts detected in endometrial tissues of patients treated with tamoxifen. Cancer Res 1999;59:2091-5.
14. Gherman RB, Parker MF, Macri CI. Granulasa cell tumor of the ovary associated with antecedent tamoxifen use. Obstet Gynecol 1994;84:717-9.
15. Cremer DW, Welch WR. Determinations of ovarian cancer risk. II. Inferences regarding pathogenesis. J Natl Cancer Inst 1983;71:717-21.
16. Gerhard I, Runnebaum B. Comparison between tamoxifen and clomiphene therapy in women with anovulation. Arch Gynaecol 1979;227:279-88.
17. Rutqvist LE, Johansson H, Signomklao T et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 1995;87:645-51.
18. Fisher B, Costantino JP, Redmond CK et al. Other NSABP Contributors. Endometrial cancer in tamoxifen-treated breast cancer patients: finding from the national surgical adjuvant breast and bowel project (NSABP) B-14. J Natl Cancer Inst 1994;86:527-34.
19. Cook LS, Weiss NS, Schwartz SM et al. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. J Natl Cancer Inst 1995;87:1359-64.
20. McGonicle KF, Vasilev SA, Odom-Maryon T, Simpson JF. Ovarian histopathology in breast cancer patients receiving tamoxifen. Gynecol Oncol 1999;73:402-6.
21. De Waard F. In Uterine Corpus in Cancer Epidemiology and Prevention. Schottenfield D and Fraumeni JF (eds). Philadelphia: WB Saunders 1982; 901-8.
22. Lonning PE, Johannessen DC, Lien EA et al. Influence of tamoxifen on sex hormones, gonadotropins and sex hormone binding globulin in postmenopausal breast cancer patients. J Steroid Biochem Mol Biol 1995;52:491-6.
23. Simon WE, Albrecht M, Hansel M et al. Cell lines derived from human ovarian carcinomas: growth stimulation by gonadotrophic and steroid hormones. J Natl Cancer Inst 1983;70:839-45.
24. Shiffenbauer YS, Abramowitch R, Meir G et al. Loss of ovarian function promotes angiogenesis in human ovarian carcinoma. Proc Natl Acad Sci USA 1997;94:13203-8.
25. Kohn EC. Angiogenesis in ovarian carcinoma: a formidable biomaker. Cancer 1997;80:2219-21.
26. McCluggage WG, Bryson C, Lamki H, Boyle DD. Benign, borderline, and malignant endometrioid neoplasia arising in endometriosis in association with tamoxifen therapy. Int J Gynecol Pathol 2000;19:276-9.
27. Okugawa K, Hirakawa T, Ogawa S et al. Ovarian endometrioid adenocarcinoma arising from an endometriotic cyst in a postmenopausal woman under tamoxifen therapy for breast cancer. Gynecol Oncol 2002;87:231-4.
28. Fallahzadeh H, Dockerty MB, Lee RL. Leiomyoma of the ovary: Report of five cases and review of the literature. Am J Obstet Gynecol 1972;113:394-8.
29. Kleitsman RJ. Ein Beitrag zur Kenntnis der Leiomyome des ovariums. Acta Obstet Gynecol Scand 1950;29:161-74.
30. Wellman KF. Leomyoma of the ovary: Report of an unusual case and review of the literature. Can Med Assoc J 1961;85:429-32.
31. Tsalacopoulos G, Tiltman AJ. Leiomyoma of the ovary. Am J Obstet Gynecol 1972;113:1142-4.
32. Vierhout ME, Pijpers L, Tham M. Leiomyoma of the ovary. Acta Obstet Gynecol Scand 1990;69:445-7.