RESEARCH COMMUNICATION

Evaluation of Ovarian Cysts in Breast Cancer Cases on Tamoxifen

Malihe Hasanzadeh Mofrad[1]*, Fatemeh Homaei Shandiz[2], Fatemeh Vahid Roodsare[1], Toktam Moghiman[1]

Abstract

Purpose: The anti- estrogen drug, tamoxifen, is one of the most important medications used in the treatment of both advanced and localized breast cancer. However, such tamoxifen use may have some risks related to the endometrium and ovaries.We followed a group of women with breast cancer on tamoxifen for the development of ovarian cysts. Methods: Based on a cross sectional study, 35 pre and post menopausal patients with breast cancer on tamoxifen were followed by pelvic exam and vaginal ultrasonography for 3 cycles of 3 month intervals; occurrence and outcome of ovarian cysts were evaluated. Results: Of the 35 tmoxifen-treated patients enrolled in this study, 21 were postmenopausal and 14 were premenopausal .Their average age was 48.1±8.7 (range: 29-65 yrs) years. The mean duration of tamoxifen therapy was 30.5± 14 months (range: 12-60 months). Ovarian cysts were diagnosed in 12 (34.3%) patients, with surgery required in 6; pathological examination revealed malignancy in two cases. Conclusion: Development of ovarian cysts is a rather frequent event in women with breast cancer on tamoxifen. The majority of cysts are simple, which may resolve spontaneously or with discontinuation of tamoxifen, but malignancy needs to be ruled out.

Key Words: Ovarian cyst - tamoxifen - breast cancer - ovarian cancer

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Introduction

Tamoxifen is a synthetic, non-steroidal, antiestrogenic drug (agonist-antagonist of Estrogen receptor) which is widely used for early and metastatic breast cancer patients with positive estrogen receptor proteins. Tamoxifen is one of the most important medications used in the treatment of both advanced and localized breast cancer (Early Breast Cancer Trialists,1998). Since 1977, the FDA has gradually broadened the indications for the use of tamoxifen to include treatment and adjuvant treatment of pre- and post – menopausal women with breast cancer irrespective a receptor or nodal status. The most recent National Surgical Adjuvant Breast and Bowel Project (NSABP B-20) concluded that combination of tamoxifen and chemotherapy reduces the risk of recurrence as well as the incidence of contralateral breast cancer (Fisher et al.,1996; Seoud et al., 2001).

Use of tamoxifen, as a preventive treatment in healthy women at high risk (familial hereditary breast cancer) for developing breast cancer, revealed a 45% decrease in the incidence of primary breast cancer after a mean duration of 3.6 years of using tamoxifen. In situ cancers were also less in patients on tamoxifen (31 versus 59, cases) (Wickerman et al.,1998).

Tamoxifen acts as an agonist of the estrogen receptor in ovary and endometrium. Some risks related to endometrial cancer have been described in tamoxifen-treated breast cancer patients (Assikis and Jordan,1995). Tamoxifen stimulates ovarian steroidogenesis in premenopausal women (Swerdlow and Jones, 2007). Tamoxifen's estrogen- like action on the ovary may potentially stimulate either ovarian enlargement or the development of ovarian pathological conditions (Cohen,1998). Thus the incidence of benign ovarian pathologies in breast cancer patients on tamoxifen were found to be higher than that reported for similar pathologies in controls or among non- selected, asymptomatic and untreated women (Cohen, 1998).

The purpose of the present prospective study was to follow a group of women with breast cancer on tamoxifen for the occurrence and outcome of ovarian cysts.

Materials and Methods

We conducted a prospective clinical study to evaluate the effect of tamoxifen administration on the ovaries of women with breast cancer.

Between January 2002 through December 2004, 35 breast cancer patients on tamoxifen were followed in the gynecology-oncology clinic of Ghaem Hospital with an investigative protocol. All the patients were treated with 10 mg twice daily and had a normal sonography at starting tamoxifen therapy.

*[1]Gynecology Oncology, Gynecologic Health Research Center and Cancer Research Center, [2]Radiation Oncology Department, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran *For Correspondence: HasanzadehMofradM@mums.ac.ir*

The patients were excluded from the study if they had a history of bilateral-oophorectomy or ovarian cyst before starting tamoxifen therapy.

Menopause was defined as amenorrhea of 12 months duration and FSH> 20 mIu/ml. Patients were monitored periodically at 3 month intervals with pelvic ultrasound and bimanual gynecological examination. Transvaginal ultra sonographic examination with a SMHZ high resolution endovaginal transducer included measurements of ovarian size and the presence of ovarian pathologies. If sonography reported a simple cyst, the decision was made according to the patient's menopausal condition. If its diameter was less than 8 cm and 5 cm in premenopausal or postmenopausal women respectively, sonography and physical examination assessment were repeated one month later. We performed a routine follow up if the tumor vanished or got smaller in size, but if it increased in size or remained the same, treatment with tamoxifen was stopped. These patients were assessed one month after cessation of tamoxifen and if they showed no response, GnRH agonist (3.75 mg) was administrated. The patient underwent surgery if they no benefit from 1 month of GnRH agonist treatment was observed.

We considered surgical intervention as the first step in women with persistent cysts, large bilateral or complex cysts (multiloculated and/or solid elements, excrescences or associated with ascites). The Student's t-test, Chi square test and Anova table test were used in data analyses. A $p<0.05$ was considered statistically significant.

Results

Thirty five women, who were being treated with tamoxifen as an adjuvant therapy for breast cancer, were enrolled in the study. Their mean age was 48.14±8.73 years (range: 29-65 yrs). Mean parity of the patients was 3.11± 2.4(range: 0-8), 60% and 40% of patients were in their postmenopausal and premenopausal period, respectively. Mean age of menopause was 47.19± 2.93 years (range: 42-53 years).

The primary treatment in all patients was modified radical Mastectomy, which showed non-metastatic breast cancer (stage I-II). After this surgical procedure they were treated with tamoxifen either with chemotherapy and radiotherapy. Tamoxifen was administered orally 10 mg twice daily. None of them received any oral contraceptives or hormone replacement therapy. Mean tamoxifen therapy duration was 30.48± 14 (range: 12-60) months in the breast

Table 1. Characteristics of Breast Cancer Patients Experiencing Cyst Formation during Tamoxifen Therapy

Case no.	Age (year)	Menopausal status	Cyst (mm)	Symptoms	Result and Pathology Findings
1	41	Premenopausal	53x40	None	Resolved after discontinuation of tamoxifen -
2	34	Premenopausal	34x29	None	Resolved after discontinuation of tamoxifen and GNRH -
3	40	Premenopausal	39x36	Bleeding	Resolved after discontinuation of tamoxifen and GNRH -
4	43	Premenopausal	33x29	None	Laparotomy Krukenberg
5	45	Premenopausal	52x72	None	Resolved after discontinuation of tamoxifen -
6	46	Premenopausal	35x43	None	Resolved after discontinuation of tamoxifen and GNRH
7	40	Premenopausal	14x22 30x17	None	Laparotomy Serous cyst adenoma
8	37	Premenopausal	44x35	Echogenic	Laparotomy Endometriosis
9	42	Premenopausal	60x50	Echogenic	Laparotomy Serous cyst adenoma
10	52	Postmenopausal	40x39	None	Laparotomy Serous cyst adenoma
11	52	Postmenopausal	60x70	Ascites	Laparotomy Serous adenocarcinoma
12	53	Postmenopausal	29x33	None	Resolved after discontinuation of tamoxifen -

Table 2. Review of Ovarian Incidence Rates and Pathologies associated with Tamoxifen

Menopausal status Post	Pre	Diagnosis and Complications	Incidence rate	Publication
0	7	- -	7/84	Sawaka et al, 1986
0	1	Luteinized cyst, necrotic ovaries	1 case	Jolles et al, 1990
0	1	Luteinized cyst, operated for fibroids	1 case	Dilts et al, 1992
0	1	Follicular cyst, torsion	1 case	Terada et al, 1993
0	1	Luteinized cyst	1 case	Anteby et al, 1993
0	1	Luteinized cyst, torsion	1 case	Barbieri et al, 1993
1	0	Granulosa cell tumor, rupture/acute abdomen	1 case	Gherman et al, 1994
0	5	Functional cyst	5 cases	Cohen et al, 1994
0	2	Functional cyst	2 cases	Shulman et al, 1994
-	-	Simple cysts	5 cases	Hochner-Celnikier et al, 1995
5	6	Simple /chocolate cyst, 3 cases operated for fibroids	11/95	Shushan et al, 1996
1	0	Endometrioid ovarian carcinoma, enlarged abdomen	1 case	Kuo et al, 1997
2	15	Cysts and two cancers	17/397	Oren et al, 1997
24	0		24/67	Mourits et al, 1999
4	14	Serous cyst adenoma, disappeared spontaneously	18/72	Seoud et al, 2001
1	0	Endometrioid ovarian carcinoma	1 case	Okugawa et al, 2002
32	0	Various	32/332	Cohen et al, 2003
1	28	Functional ovarian cyst,Ovarian enlargement	29/150	Metindir et al, 2005
0	2	Serous cystadenoma, elvic pain, ovarian mass	9/51	Inal et al, 2005
2	9	Various, abnormal uterine bleeding, ascities	121/35	Hasanzadeh et al, 2010

cancer patients and 23.5± 10.37 months in the patients with ovarian cysts (p=0.046).

Overall,12 of 35 (34.3%) patients on tamoxifen developed ovarian cysts during the observation period .The mean age of women who developed ovarian cyst was significantly lower than the mean age of women who did not [43.58± 6.2 years (range 34-53 yrs) and 50.52± 9.01(range 29-65) years, respectively (p=0.023)].

Cysts were detected in 9 of 14 pre-menopausal women (64.3%) and 3 of 21 post-menopausal women (14.3%) (p=0.002). Table 1 shows the data of the patients who developed ovarian cysts.

The majority of ovarian cysts were unilateral (83.4%), whereas 16.6% of patients had bilateral ovarian cysts.

Most ovarian cysts were simple and asymptomatic. On follow up visits, five premenopausal and one postmenopausal patient with cysts were managed conservatively. The ovarian cysts resolved in 3 patients after withheld tamoxifen therapy, in the other three cases, the cysts resolved after GnRH therapy.

Six (17.1%) of the 35 patients underwent surgery due to characteristics of the ovarian cysts. Two of these six patients who underwent laparatomy were in their postmenopausal and four were in their premenopausal period. Histological evaluation of the removed ovaries in postmenopausal patients revealed Serous cyst adenoma or well-differentiated Serous adenocarcinoma .

Four of the premenopausal women underwent laparatomy and pathological examination revealed serous cysts adenoma, endometriosis and krukenberg tumor. Sonographic finding in the patient with krukenberg tumor was bilateral hypo- echoic ovarian mass.

Discussion

This study clearly indicates that the development of ovarian cysts is common during tamoxifen administration. We noticed that 12 of 35 tamoxifen-treated women had ovarian cysts. They occur more commonly in premenopausal women. Two of our cases had ovarian cancer (early and metastatic) .This study demonstrates that we must consider ovarian malignancy in the differential diagnosis of ovarian cyst in breast cancer patients receiving tamoxifen, premenopausally.

Tamoxifen is a nonsteroidal antiestrogen that is demonstrably effective in the treatment of early and metastatic breast cancer (Early Breast Cancer Trialists, 1998). Up to 1985, a low incidence of side effects was noted in all reports on tamoxifen; after 1985 many authors reported significant links between tamoxifen treatment and endometrial cancers and these were followed by reports of a positive correlation between tamoxifen treatment and ovarian cystic enlargement. The cystic enlargement of an ovary in a patient with breast cancer creates a serious clinical conflict. Cystic enlargement of the ovaries can either be the result of functional cysts (in premenopausal women) or of metastases from the primary breast cancer, or due to a primary ovarian malignancy (women with breast cancer have quite a high risk of ovarian carcinogenesis) (Inal et al., 2005).

The mechanism of action of tamoxifen in stimulating the development of ovarian cysts is not yet fully known. It is believed that tamoxifen competes with estrogen receptors, leading to a decline in circulating estrogen levels and thus increasing the level of gonadotropin releasing hormone, which stimulates the pituitary gonadotropins (Jolles et al., 1990). In postmenopausal women direct stimulation of the ovaries is more likely to explain the development of ovarian cysts.

There are some studies and case reports on ovarian cysts that developed during tamoxifen treatment; Mourits (1999) reported that 24 of 67 tamoxifen-treated pre-menopausal women had cystic enlargement of the ovaries. In our study 9 of 14 (64.2%) tamoxifen-treated pre menopausal women had ovarian cysts in which the mean time of tamoxifen treatment in these women was 30 months, whereas the cysts developed after 12 and up to 48 months of treatment initiation. In Cohen's report, 32 (14%) of 332 postmenopausal women with breast cancer who were treated with tamoxifen had simple ovarian cysts. Three (9%) of these patients underwent surgery. Histological evaluation of the removed ovaries revealed simple ovarian cyst, well-differentiated ovarian carcinoma, and metastatic adenocarcinoma (Cohen et al.,2003), in line with our results; of 21 postmenopausal women,3 (14.3%) had ovarian cysts. Histological evaluation of the removed ovaries in postmenopausal patients revealed serous cyst adenoma and well-differentiated serous adenocarcinoma. Seoud et al (2001) reported that 18 (25%) of 72 tamoxifen-treated women with metastatic breast carcinoma had ovarian cysts. The mean age of women who developed ovarian cysts was significantly lower than those who did not. Our results were similar to this study. Metindir et al (2005) reported that 29 (19.3%) cases of a group of 105 tamoxifen-treated breast cancer patients had ovarian cysts. Cysts were detected in 28 of 57 pre-menopausal women (49.1%) and 1 of 93 post-menopausal women (1.1%).

Numerous ovarian cyst pathologies based on menopausal status have been reported in differential studies so far (Table 2). Several investigators have reported luteinized, follicular and chocolate cysts (Cohen et al, 1994, Shulman et al., 1994, Hochner- Celnikier et al., 1995, Shushan et al., 1996) while others have reported ovarian malignancies including an endometriod carcinoma (Kuo et al., 1997, Okugawa et al., 2002) and granulosa cell tumor (Gherman et al., 1994). Oren et al (1997) reported two ovarian cancers among 397 patients on tamoxifen but concluded that the overall incidence was not increased. In the study by Cohen et al (2003), two (6%) of the 32 patients with ovarian cysts who were operated, had well-differentiated ovarian carcinoma and metastatic adenocarcinoma of the breast cancer. In our study, we detected two cases of ovarian carcinoma, in which one postmenopausal case had a large cyst and the other premenopausal case had bilateral ovarian cysts. Morphology indexing is one of the adjuvant methods capable of increasing the positive predictive value of transvaginal ultrasonography .Morphologic characteristics of ovarian tumors are related directly to the risk of malignancy. It is of important to note that Unilocular cystic tumors are usually benign, whereas bilateral or complex

ovarian tumors with solid or papillary components are malignant, surgical intervention should be considered in women with such findings.

In the literature there are no specific recommendations regarding the treatment of ovarian cysts in tamoxifen - treated women. Most patients, especially those with small ovarian cysts, are best managed with close observation only; Temporary discontinuation of tamoxifen is also recommended. Another approach is the administration of GnRH agonists which has been demonstrated to be successful in resolving these cysts (Shulman et al., 1994, Shushan et al., 1996). We do not like discontinuation of tamoxifen in breast cancer women and a new chemoprevention regimen in premenopuse is GnRH agonist . The ovarian cysts disappeared in three of our cases after receiving GnRH agonist.We must consider this option in treating of ovarian cyst in breast cancer.

In conclusion, in cases with ovarian cyst formation during tamoxifen treatment of breast cancer, discontinuation of tamoxifen and administration of GnRH is quite a reasonable way to proceed in most patients. Surgical intervention should be carried out when cysts are persistent, bilateral, large or complex.

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