Ovarian Tumors in 6 Patients Using Tamoxifen for Breast Cancer

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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 have developed 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

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CASE REPORT

Ovarian Tumors in 6 Patients Using Tamoxifen for Breast Cancer

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-pituitary-ovarian axis (2). Very little is known about the effects of tamoxifen on the ovary.
Several reports suggest that there may be an association between 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 metabolite 4-OH-tamoxifen have a direct antiproliferative effect on human ovarian carcinoma specimens (12). Long-term treatment with 4-OH-tamoxifen has also been associated with the enhancement of antiapoptotic 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 standard dose FEC (5-fluorouracil, epirubicin and cyclophosphamide) or FAC (5-fluorouracil, adriamycin and cyclophosphamide) or CMF (cyclophosphamide, 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 standard dose FAC. She had been taking tamoxifen citrate 20 mg/day for 8 months. Pelvic examination revealed a right adnexal mass. Total abdominal hysterectomy and bilateral salpingo-oophorectomy 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 standard dose FEC and radiotherapy. 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 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 fibrothecal hyperplasia.

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 standard 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 not elevated (364 IU/ml). Transvaginal ultrasonography showed 55x44 mm in diameter cyst with papillary projection on right ovary. Total abdominal hysterectomy and 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 standard dose CMF and radiotherapy. She had been taking tamoxifen citrate 20 mg/day for 48 months. Pelvic examination revealed a right adnexal mass. 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 standard 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 standard 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 occurrence 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

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

*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 use is not associated with the occurrence 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 malignant 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 distinctly 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). Histogenetically, 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 one patient with cortical fibrothecal hyperplasia in this study. We demonstrated that the possible effect of tamoxifen in the growth of stromal edema and cortical fibrothecal hyperplasia which occurred 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