Reproductive tract pathology in asymptomatic women treated with tamoxifen

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Summary

Purpose: To determine the long-term effects of tamoxifen on the female reproductive tract in patients with breast cancer.

Methods: Forty-nine patients with breast cancer receiving tamoxifen longer than two years were analyzed. All the patients underwent pelvic examination, pap smear, transvaginal ultrasonography, serum CA 125 and dilatation and curettage.

Results: There were 16 patients with genital system pathology. Three of them had atypical Pap smears, one with cervical carcinoma and the other two with chronic cervicitis. Two significant ovarian pathologies were found. These were ovarian fibroma, and unilateral dermoid cyst. There were three patients with endometrial hyperplasia without atypia. Uterine myoma was encountered in seven of the cases. Only one patient had elevated CA 125 levels despite normal genital examination findings.

Conclusion: Since no significant genital pathology attributable to tamoxifen therapy could be detected, the follow-up for gynecologic pathologies in breast cancer patients receiving tamoxifen therapy may be individualized.

Key words: Tamoxifen; Breast cancer; Endometrial hyperplasia.

Introduction

Tamoxifen, a nonsteroidal antiestrogen, is one of the most valuable treatment alternatives for breast cancer patients, especially those with positive estrogen receptors [1-3]. It has also been used for palliation in both premenopausal and postmenopausal women with advanced or recurrent breast cancer. Adjuvant tamoxifen therapy in early stage breast cancer became common in the 1980s, and has been shown to improve disease-free survival for women older than 50 years [4]. However, our knowledge regarding the long-term effects of tamoxifen is still limited. Its antiestrogenic effect appears to be due to its ability to bind cytoplasmic estrogen receptors [5]. Although tamoxifen acts primarily as an antiestrogen, it also appears to exert a mild estrogenic effect as well. Postmenopausal women who receive tamoxifen may show estrogen-like effects on the vaginal epithelium and the endometrium. The combined estrogen agonist and antagonist property of tamoxifen raised the question that it may increase the risk of endometrial hyperplasia and cancer. In recent years some cases of endometrial cancer and benign endometrial changes in breast cancer patients receiving tamoxifen have been reported [6-10].

Materials and Methods

The study group consisted of 49 patients who had received tamoxifen therapy (20 mg/d) for more than two years as adjuvant therapy for breast cancer in Hacettepe University Hospital during 1998 and 1999.

All the patients underwent pelvic examination, Pap smear, transvaginal ultrasonography, serum CA 125 and fractional curettage. Ultrasonography was used to measure the ovarian and uterine sizes and endometrial thickness. The cut-off level for CA 125 was 35 U/ml.

The mean age of the patients were 51.7 years (range: 35-72). Thirty-six patients (73.5%) were postmenopausal. The patients were under regular follow-up for breast cancer and all were disease-free. Two of them had a relative (sister and mother) with breast cancer (4.0%), and one had a sister with colon cancer (2.0%). Thirty-one (63.3%) had taken adjuvant chemotherapy and radiotherapy, three patients (6.1%) had only radiotherapy, ten of the patients (20.4%) had only chemotherapy and five patients (10%) had not undergone any adjuvant therapy.

Results

There were 16 patients with reproductive tract pathologies (Table 1). Three (6.1%) of the 49 patients had atypical smears. One of them (age 70) had stage IB1 invasive cervical cancer. The patient underwent radical hysterectomy and lymphadenectomy and postoperative adjuvant radiotherapy. The other two patients (ages 65 and 70) were found to have chronic cervicitis, one with endocervical polyps.

In six (12.2%) of the cases, the ovarian size was more than 8 cm^3. One of them was a dermoid cyst. The patient was 38 years old with a history of left salpingo-oophorectomy eight years before. She underwent total abdominal hysterectomy and right salpingo-oophorectomy. The other case was a 43-year-old woman with an ovarian fibroma. She underwent laparoscopic oophorectomy. All the other four cases had simple cystic ovaries, as confirmed by ultrasonographic and Doppler studies and they had normal CA 125 values.

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The uterine size was found larger than normal in ten cases (20.4%). There were single or multiple fibroids in seven of them (14.2%), and three of those seven patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and one patient had vaginal hysterectomy and bilateral salpingo-oophorectomy due to coexistence of significant pelvic relaxation.

Only a 50-year-old patient had elevated CA 125 levels (49 U/ml), but her genital examination was absolutely normal. She was still under follow-up without any problems.

Mean endometrial thickness was 5.86 mm (range: 1-19 mm). Ten patients (20.4%) had an endometrial thickness more than 8 mm. There were three (6.1%) patients with simple endometrial hyperplasia without atypia. The endometrial thickness values in these patients with endometrial hyperplasia were 8, 8 and 6 mm, respectively. Tamoxifen was replaced with progesterone treatment for six months. Follow-up biopsies were all normal. The most common endometrial change encountered in the study group was proliferative endometrium (Table 2).

Table 1. — *Tamoxifen and genital pathologies.*

	No	%
Atypical smear	3	6.1
Cervical cancer	1	2.0
Dermoid cyst	1	2.0
Ovarian fibroma	1	2.0
Uterine myoma	7	14.2
Endometrial hyperplasia	3	6.1

Table 2. — *Tamoxifen and endometrial changes.*

	No	%
Endometrial hyperplasia	3	6.1
Proliferative endometrium	23	46.9
Cystic changes	7	14.3
Atrophic changes	13	26.6
Normal glandular epithelum	3	6.1

Discussion

The antiestrogenic activity of tamoxifen is supposed to be mediated by its competitive binding to the estrogen receptor, translocation with receptor to the nucleus, and subsequent decreased replenishment of the cytoplasmic receptor [11]. Tamoxifen, however, possesses estrogen agonists properties in addition which may be mediated by its occupying that receptor in postmenopausal women with little estradiol available [10]. These effects are evident in the female genital tract with estrogenic effects noted in vaginal epithelium and endometrium [12-14].

Although 6.1% of the patients demonstrated abnormal cytology in this series, there is no reported correlation between tamoxifen treatment and cervical cancer. Rayter found no increase in the incidence of cervical dysplasia in patients on tamoxifen therapy [15]. The reported case with cervical cancer, thus, was evaluated to be incidental.

There were no significant increases of ovarian size in patients taking tamoxifen therapy in this series. Only 12.2% of the patients had increased ovarian size with two significant pathological findings. One of them was a dermoid cyst and the other one was a fibroma. Their relation with tamoxifen use is evaluated to be unclear and probably incidental. The patients were premenopausal (ages 38 and 43). However, tamoxifen has been shown to induce ovarian steroidogenesis in premenopausal women [16-18]. It is not clear whether this hypersecretory state can lead to adverse ovarian pathology, but tamoxifen has been associated with an increased incidence of fibroid ovaries and ovarian cysts in a study by Rayter *et al.* [16]. In our group there was one patient with an elevated CA 125 level which was evaluated to be insignificant.

Lahti *et al.* reported uterine fibroids were more common in the tamoxifen group [19]. Present incidence of uterine myoma as 14.2% correlates well with the literature data. Furthermore, there are reports of three cases of uterine sarcomas in the Scottish Trial in the review of this data by Malfetano and one sarcoma among the cases reported by Hardell [20, 21]. Since the previous history of the patients with uterine myoma is lacking, it is hard to conclude that these fibroids were due to tamoxifen treatment.

The relationship between tamoxifen and endometrial cancer is currently receiving a great deal of attention in the literature. The strongest data that exist regarding the association between tamoxifen and cancer of the uterine corpus were published by Fornander *et al.* in 1989. They found 13 new endometrial adenocarcinomas in the tamoxifen treated group, yielding a relative risk of 6.4 [22]. Review of the South Western Oncology Group data on 966 patients revealed four endometrial cancers in tamoxifen-treated subjects, compared with none in controls [1]. Anderson *et al.* also showed a relatively higher risk for developing endometrial cancer in the tamoxifen group than in controls [23]. Despite the cumulative data [1, 22-26] indicating a correlation between tamoxifen and endometrial cancer, we were not able to find endometrial cancer in this series. There were only three cases of simple endometrial hyperplasia without atypia. All of these patients had an endometrial thickness more than 5 mm by transvaginal ultrasonography. This pathologic finding was reversed after stopping tamoxifen treatment and a trial of progesterone for six months. Love *et al.* also do not suggest routine screening of asymptomatic women due to low frequency of significant findings [27]. Therefore, currently, neither endometrial sampling nor ultrasound evaluation just because an asymptomatic individual is on tamoxifen does not seem to be cost effective. The follow-up for gynecologic pathologies in breast cancer patients receiving tamoxifen therapy may be individualized.

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