Uterine pathologies in patients undergoing tamoxifen therapy for breast cancer: ultrasonographic, hysteroscopic and histological findings

M. Le Donne, M. Lentini[1], L. De Meo[2], V. Benedetto, M. Misiti[3]

Department of Gynecological, Obstetric Sciences and Reproductive Medicine
[1]Department of Human Pathology, [2]Department of Financial, Social and Environment Economics
[3]Oncological Surgery Unit, University of Messina (Italy)

Summary

Purpose of investigation: To evaluate endometrial abnormalities by ultrasonography, hysteroscopy and biopsy in postmenopausal patients treated with tamoxifen as adjuvant therapy for breast cancer.

Methods: The study was carried out on 113 patients who underwent vaginal ultrasonography, hysteroscopy and endometrial biopsy.

Results: There was a significative relation between ultrasonographic and hysteroscopic features ($p < 0.001$); 58 polyps were diagnosed at hysteroscopy, although 35 were not found at ultrasonography. A significant relation between ultrasonographic and histological findings was also documented ($p < 0.005$). A significant relation between histological findings and symptomatology was found ($p < 0.05$), although pathologies were also present in asymptomatic women.

Conclusions: These results show that long-term tamoxifen therapy in breast cancer patients is associated with a higher incidence of uterine pathology. No significant relation has been documented between duration of treatment and grade of endometrial lesion ($p > 0.05$). Ultrasonography alone is useful in asymptomatic patients because it selects patients with increased endometrial thickness who should undergo hysteroscopy. Hysteroscopy is more accurate in detecting polyps, hyperplastic and neoplastic changes. Asymptomatic tamoxifen treated women should be evaluated as symptomatic patients.

Key words: Breast cancer; Tamoxifen; Transvaginal ultrasound; Hysteroscopy; Endometrial cancer.

Introduction

Tamoxifen is a nonsteroidal antiestrogen with weak estrogenic action that has been widely used as adjuvant therapy for breast cancer in the last 20 years [1]. Furthermore its use for protection against breast cancer in women at risk, is also being explored in pilot studies [2]. Many studies showed an increased incidence of endometrial cancer in patients treated with this drug [3-5], and the association between tamoxifen administration and uterine pathologies is well documented: typical and atypical glandular hyperplasia, endometrial polyps, uterine fibroids, adenocarcinoma and sarcoma [1, 6-9]. The risk seems to be highest after long-term use [6, 8]. Furthermore the long-term tamoxifen users have a worse prognosis of endometrial cancers [5-7]. Increasingly endovaginal ultrasonography has improved the measurement and characterization of the endometrium, in a variety of clinical situations, but reported measurement of endometrial thickness up from 6 to 8 mm have been subsequently associated with inactive endometrium on biopsy [10-14]. Hysteroscopy with biopsy is the most sensitive and specific method to get a sure diagnosis, but is an invasive procedure [15, 16].

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Methods

Between January 2000 and December 2004, 113 women being treated with tamoxifen for breast cancer, who attended our department for gynecological assessment, were included for this study. All the patients were peri/postmenopausal with no prior hormone therapy and/or gynecological pathology before the diagnosis of breast cancer. The mean duration of the treatment was 38.77 months; the daily dose was of 20 mg in 75.2% of the patients, 30 mg in 21.23%, < 20 mg in 1.8% and 40 mg in 1.77%. Fifty-five patients were asymptomatic, while the remaining 58 presented abnormal uterine bleeding. Transvaginal ultrasonographic evaluation was performed in 95 patients, using a 5.0 mHz Aloka 500 system. The widest endometrial thickness was recorded on the midline sagittal scan by including the double layer of the endometrium. Hysteroscopy with endometrial biopsy was performed in 108 patients and failed in five cases because of cervical stenosis. In these patients endometrial biopsy was obtained by curettage. In eight cases the endometrial material was insufficient or scanty for histological diagnosis. Correlations between ultrasonographic, hysteroscopic and histological features were performed using the chi-square test.

Results

The age of the patients ranged from 33 to 83 years with a mean of 61.58 years. They were multiparas. The mean age at menopause was 48.9 years. Ultrasonographic, hysteroscopic and histological findings are summarized in Table 1.

Table 1. — *Ultrasonographic, hysteroscopic and histological features.*

		No.	%
Ultrasonography [1]	Endometrial thickness < 5 mm	1	11.58
	Endometrial thickness 5-8 mm	26	27.37
	Endometrial thickness > 8mm	23	28.21
	Polyp	27	28.42
	Suspected lesion	8	8.42
Hysteroscopy [2]	Atrophy	22	20.40
	Vascular congestion	29	26.80
	Polyp	66	61.11
	Suspected lesion	9	8.33
Histology [3]	Atrophy	16	15.40
	Hypotrophy	20	19.23
	Hyperplasia	7	6.73
	Polyp	44	42.30
	Cancer	17	16.35

[1]Total no. of ultrasonographies 95; [2] Total no. of hysteroscopies 108; [3] Total no. of histological findings 104.

Among the 95 patients evaluated by ultrasonography, the endometrial thickness was < 5 mm in 11, between 5 and 8 mm in 26, and > 8 mm in 23 (in these last cases at the hysteroscopic and histological examination atrophic endometrium was found). Polyps were suspected in 27 cases; in eight cases suspected lesions were visualized.

At hysteroscopy polyps were present in 66 patients and in 30 cystic atrophy was associated. Atrophy alone was visualized in 22 cases, vascular congestion in 29 cases, hyperplastic lesions in three cases and neoplastic lesions were suspected in nine cases.

Histological findings included atrophy in 16 cases, microcystic hypotrophy in 20 cases, hyperplasia in seven cases, endometrial polyps in 44 cases and cancer in 17 cases.

The histotypes of cancer were represented mostly by endometrial adenocarcinomas including ten endometrioid and three adenosquamous cancers; while three, among 17, consisted of high-risk histological subtypes including one papillary serous carcinoma and two mesodermal mixed tumors. One squamous cervix carcinoma was also detected. The documented endometrial cancer histotypes with a poor prognosis were not related to the dosage or duration of tamoxifen therapy; they occurred after 36, 60 and 66 months of therapy, respectively.

Comparison between bleeding patients and asymptomatic ones regarding endometrial thickness is summarized in Table 2; there were no significant differences between the two groups ($p > 0.05$) .

Table 3 shows the presence of a significant relation between histological findings and symptomatology ($p < 0.05$). On the other hand, pathologies were also present in asymptomatic women.

Table 2. — *Correlation between ultrasonographic features and symptomatology.*

	Asymptomatic	Symptomatic	No.	%
Endometrial thickness < 5 mm	3	8	11	11.58
Endometrial thickness 5-8 mm	12	14	26	27.37
Endometrial thickness > 8 mm	12	11	23	24.21
Polyp	15	12	27	28.42
Cancer	3	5	8	8.42
Total	45	50	95	100

Chi square = 3.05; $p > 0.05$.

Table 3. — *Correlation between histological findings and symptomatology.*

	Atrophy	Hypotrophy	Hyperplasia	Polyp	Cancer	No.
Asymptomatic	8	7	3	28	3	49
Symptomatic	8	13	4	16	14	55
Total	16	20	7	44	17	104

Chi square = 12.03; $p < 0.05$.

Table 4. — *Correlation between ultrasonographic and hysteroscopic findings.*

Ultrasonography	Hysteroscopy				
	Atrophy	Polyp	Suspected lesion	No.	%
Endometrial thickness < 5 mm	5	6	0	11	11.58
Endometrial thickness 5-8 mm	12	13	1	26	27.37
Endometrial thickness > 8 mm	9	11	3	23	24.21
Polyp	2	23	2	27	28.42
Suspected lesion	0	5	3	8	8.42
Total	28	58	9	95	100
%	29.47	61.05	9.47		

Chi square = 23.16; $p < 0.01$.

There was a significant relation between ultrasonographic and hysteroscopic features ($p < 0.001$), as summarized in Table 4. Endometrial thickness was increased if polyps were present, but out of 28 cases of endometrial thickness > 5 mm, 21 were cystic atrophy at hysteroscopy. Nevertheless 58 polyps were diagnosed at hysteroscopy, 35 of which were not found at ultrasonography. Of nine suspected focal lesions visualized at hysteroscopy, three were also suspected at ultrasound; two were polyps and four were diagnosed as endometrial thickness more than 5 mm.

There was also a significant relation between ultrasonographic and histological findings ($p < 0.005$), as shown in Table 5. Among 16 cancer cases, five were suspected and six were diagnosed as polyps at ultrasonography (some of these were carcinomatous); in four cases the endometrial thickness was > 8 mm and only in one case < 8 mm. On the other hand, in many cases with increased endometrial thickness, there was atrophy or microcystic hypotrophy on biopsy.

There was no significant relation between duration of therapy and endometrial thickness, or histopathological findings ($p > 0.05$). Women treated for longer than 48 months showed a higher incidence of endometrial polyps and cancers (two cases of cancer occurred after 11 and 12 years of treatment), than patients exposed to the drug for less than 24 months, as summarized in Table 6.

Table 5. — *Correlation between ultrasonographic and histological findings.*

Ultrasonography	Histology						
	Atrophy	Hypotrophy	Hyperplasia	Polyp	Cancer	No.	%
Endometrial thickness < 5 mm	3	6	0	2	0	11	12.64
Endometrial thickness 5-8 mm	1	7	3	11	1	23	26.44
Endometrial thickness > 8 mm	6	1	0	9	4	20	22.99
Polyp	1	3	0	15	6	25	28.74
Suspected cancer	0	0	0	3	5	8	9.20
%	11	17	3	40	16	87	100

Chi square = 47.94; $p < 0.005$.

Table 6. — *Correlation between duration of treatment and histological findings.*

Months	Histology					
	Atrophy	Hypotrophy	Hyperplasia	Polyp	Cancer	No.
0-6	1	4	1	5	2	13
7-12	3	2	0	7	2	14
13-24	3	5	0	4	1	13
25-36	5	3	0	12	1	21
37-48	2	2	1	4	1	10
> 48	2	4	4	12	10	32
N	16	20	6	44	17	103 [1]
%	15.53	19.42	5.83	42.72	16.50	100

[1] In one case the duration of treatment was not noted.
Chi square = 23.11; $p < 0.05$.

Discussion

Tamoxifen treatment is associated with an increased risk of developing endometrial cancer. The relative risk is estimated to be two- to six-fold [3, 4, 17] and increases with the duration and the cumulative dose of therapy [1, 17, 18].

The presence of endometrial pathology in 65% of our study population, confirms, in agreement with the current literature, that long-term tamoxifen use in breast cancer patients is associated with a higher incidence of uterine pathology. Several studies documented a connection between tamoxifen therapy and benign uterine pathologies (endometrial polyps, hyperplastic endometrial changes) and their incidence (3, 9, 10 times more frequently in treated patients) exceeds the incidence of endometrial cancer [19], suggesting that most of these "proliferative" effects of tamoxifen on endometrium do not progress to cancer.

There is no accordance between authors regarding the duration of tamoxifen therapy and the incidence of endometrial pathology. No relation was documented in our study between duration of treatment and grade of endometrial lesion, but the incidence of cancer was higher in patients exposed to tamoxifen for longer than four years.

The process by which tamoxifen contributes to the carcinogenesis of endometrial cancer is unknown. The findings of atypical metaplasia in often cystic atrophic endometrium is not explained by estrogenic effects, but points to antiestrogen or progesterone-like activity [20].

In Bergman's study long-term tamoxifen use was positively correlated with p53 overexpression of the endometrial tumour, inversely correlated with estrogen-receptor status, and p53-positive tumors were more often steroid-receptor negative and belonged more often to the group of malignant mixed mesodermal tumors and endometrial sarcomas [6]. The documented endometrial cancer histotypes with a poor prognosis in our study were not related to the dosage or duration of therapy.

The endometrial sequels of tamoxifen treatment necessitate adequate and prompt diagnoses. The most effective and acceptable means of undergoing long-term therapy is still debated. Asymptomatic tamoxifen treated women should be evaluated as symptomatic patients. Whether and how they should be evaluated, is another controversial problem.

Transvaginal ultrasonography is widely used to detect endometrial pathology, but postmenopausal tamoxifen users have a thicker endometrium than controls (9-13 mm compared with 4-5 mm) [21]. However there is discordance between sonographic, hysteroscopic and histological findings [10-12, 22, 23]. Cystically thickened endometrium on ultrasound in 50-90% of cases is not confirmed at hysteroscopy (atrophic endometrium) and corresponds histologically with condensated stroma and fluid-filled, cystically dilated glands lined with flattened epithelium [23] . Considering our data, ultrasonography does not seem accurate in identifying hyperplasia and polyps because both endometrial thickness and ultrasonographic features missed hyperplastic changes and polyps in a large number of cases. Furthermore it could not differentiate between a polyp which may contain a cancerous area and endometrial glandulocystic atrophy.

The great many false-positives, between 46-56% [24], that this procedure presents entails an increase in aggressive examinations.

On the other hand, hysteroscopy was more accurate in diagnoses of polyps, hyperplastic and neoplastic changes. In fact it is the only method that provides a direct view of the endometrial cavity and the possibility of performing directed biopsies for the definitive diagnosis [25].

Ultrasonography alone is useful in asymptomatic patients. If the endometrial line is irregular or the thickness exceeds 5 mm, hysteroscopy with directed biopsy is the appropriate diagnostic protocol.

We believe, in agreement with other authors [26], that these high-risk patients need this screening although the cost/efficacy ratio is not favorable.

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Address reprint requests to:
M. LE DONNE, M.D.
Dipartimento di Scienze Ginecologiche
Ostetriche e Medicina della Riproduzione
Policlinico Universitario "G. Martino",
Via Consolare Valeria
98125 Messina (Italy)