Aggressive endometrial carcinoma in a breast cancer patient treated with tamoxifen with normal transvaginal ultrasonography. Case report

F. Renard[1], *M.D.*; **M. Vosse**[2], *M.D.*; **I. Scagnol**[3], *M.D.*; **A. Verhest**[3], *M.D.*

[1]*Data Centre,* [2]*Gynaecologic Surgery Department,* [3]*Anatomopathologic Department, Jules Bordet Institute, Brussels (Belgium)*

Summary

Since tamoxifen therapy can induce endometrial disorders, surveillance schemes of women taking tamoxifen have been recommended. Transvaginal ultrasonography is a very sensitive test and therefore is often performed as a first-line screening test.

We described a very atypical case of a high stage, high grade endometrial cancer associated with tamoxifen in a 64-year-old woman with a past history of breast cancer. This women was assessed yearly by ultrasonography and Pap smear. The cancer developed on a very thin endometrium and transvaginal ultrasonography failed to detect it. The patient remained asymptomatic up to the diagnosis. Normal endometrial cells in the Pap smear test were the only signs associated with this cancer.

Surveillance strategies and significance of endometrial cells on the Pap smear are reviewed. In conclusion, TVUS can fail to detect cancers if the endometrial lining is not enlarged. In case of normal endometrial cells in the Pap smear, a careful evaluation should be performed.

Key words: Uterine neoplasms; Tamoxifen; Surveillance strategy; Pap smear; Transvaginal ultrasonography; Sensitivity.

Introduction

Tamoxifen is the hormonal treatment of choice for all stages of breast cancer [1] and has been broadly used for more than 20 years. This has been a matter of concern since randomised studies [2-4] have shown a moderate increase in the relative risk of endometrial cancers (ranging from 2 to 4) in women taking tamoxifen. In this regard, various surveillance strategies for endometrial disorders in women taking tamoxifen have been proposed to screen and treat preinvasive pathologies or early stage endometrial cancers. Because the increase in relative risk is moderate, surveillance is a controversial issue, and low-invasive surveillance strategies are currently preferred. Transvaginal ultrasonography (TVUS) is a low-aggressive and easy-to-perform examination with high sensitivity. It is often recommended as a first-line screening method, followed by a more invasive technique in case of endometrial thickness above a determined cutt-off point. In our oncological unit, breast cancer patients taking tamoxifen are followed with a yearly TVUS, completed by an outpatient hysteroscopy with endometrial sampling in case of endometrial thickness of 8 mm or more. Besides these procedures reserved for patients taking tamoxifen, all our patients are routinely followed by gynaecological examination and a Papanicolaou smear test.

We describe a case of a highly aggressive endometrial cancer, which escaped the endometrial surveillance strategy and was incidentally found by routine cytology.

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Case Report

A 64-year-old woman, gravida 3, presented at the Gynaecologic Department of the Jules Bordet Institute for a routine surveillance of endometrial disorders under tamoxifen. She had been menopausal since the age of 58 years and never took any hormonal replacement therapy. She had a history of T2N0M0 high-grade (Scarff and Bloom 9, grade III) ductal breast cancer, treated in October 1992 by quadrantectomy with axillary lymph node dissection. She also underwent adjuvant radiotherapy and received six cycles of cyclophosphamide-methotrexate-fluorouracil. She received tamoxifen for 55 months, initially at a 40 mg daily dose, and after seven months at a 20 mg daily dose, leading to a total cumulated dose intake of 37 g. Follow-up included a yearly transvaginal ultrasonography (TVUS) to assess endometrial thickness, a gynaecological exam and a Pap smear.

Table 1 shows the evolution of the clinical and paraclinical history. Routine surveillance visits preceding October 1997 did not reveal any abnormality. The patient was asymptomatic. Successive yearly TVUS measured an endometrial thickness of 7 mm, 6 mm, 6 mm and 4 mm, and all Pap smears were normal or showed rares histiocytes. In October 1997, the Pap smear showed for the first time the presence of normal appearing endometrial cells, which led to further investigation. At the same time, the patient was clinically well, and in particular, did not show any gynaecological trouble. Endometrial thickness was 4 mm at TVUS. Outpatient hysteroscopy performed under local anaesthesia showed a regular endouterine cavity with atrophic endometrium. The simultaneous endometrial biopsy confirmed endometrial atrophy without any abnormal cells. It was then decided to follow the patient at closer intervals. Six months later, in May 1998, a new TVUS showed an endometrial thickness of 3 mm. The Pap smear was now normal without any endometrial cells. The patient remained asymptomatic. In November 1998, the Pap smear revealed atypical cells

compatible with a glandular neoplasm of the endocervical canal. It was followed by a cytobrush smear which showed abnormal endometrial cells with high suspicion of endometrial carcinoma. The patient remained totally asymptomatic. A TVUS again measured an endometrial thickness of 3 mm.

Following the discrepancy between cytology and ultrasonography, the patient was admitted to hospital and underwent diagnostic hysteroscopy and D&C. Conization with CO_2 laser was performed at the same time to rule out cervical carcinoma. The pathologic examination revealed grade III endometrial endometrioïd adenocarcinoma with invasion of the endocervix and lymphatic emboli in the stroma of the cervix.

Total radical hysterectomy (Wertheim procedure) with bilateral pelvic lymph node dissection was then performed. The pathologist confirmed the diagnosis of grade III endometrial carcinoma of endometrioïd type with villoglandular architecture, invading the whole myometrium up to the serosal surface, the cervix, both parameters, both ovaries and the vagina. The ascitic fluid contained glandular malignant cells (FIGO IVB). Six pelvic nodes among ten were positive. Immunolabeling by vimentine was positive in the stromal cells and a very small number of tumoral cells. CEA was not detected. Abdominal CT showed hepatitic metastasis. She received adjuvant chemotherapy.

Discussion

We report here a case of highly aggressive endometrial cancer in a woman under tamoxifen. Interestingly, diagnosis was suspected only by cytology, without symptoms or associated signs, or any ultrasonographic increase of the endometrial lining.

Tamoxifen, a non-steroïdal antioestrogenic drug, shows some oestrogenic activity on the endometrial mucosa. Therefore, is it usually associated with a thickening of endometrial lining [5-7] and is responsible for various endometrial disorders of which most are benign [5-8]. Curiously, in this case, endometrial thickness decreased over the years of tamoxifen intake, and endometrial cancer developed with an endometrial thickness of 4 mm, although tamoxifen-associated endometrial cancers are usually associated with endometrial thickening. In a review of reported tamoxifen-associated endometrial cancers, Suh-Burgmann and Goodman did not note any case in which cancer was found in a patient with an endometrial thickness of 8 mm or less [9]. Moreover, in a series of 111 women at risk for breast cancer randomly assigned to tamoxifen or placebo, Kedar *et al.* did not find any endometrial disease below 8 mm of endometrial thickness [7]. It is therefore commonly accepted that an endometrial thickness of 8 mm as measured by ultrasonography has a high sensitivity and a high negative predictive value, meaning that few or no cancers should be missed using this cut-off. In our own review of the literature, we found only one case of endometrial cancer with an endometrial lining below 8 mm under tamoxifen, but this patient had vaginal bleeding [10].

Authors agree that a full evaluation of women with vaginal bleeding is recommended [11, 12-15]. Endometrial cancer is responsible for 15% of vaginal bleeding [16]. However, our patient did not have any vaginal bleeding and would have escaped a detection based on symptoms.

On the contrary, in asymptomatic women taking tamoxifen, the benefit of surveillance is not clear [17], since the relative risk of developing endometrial cancer under tamoxifen is moderate and the cost-effectiveness of active

Table 1. — *Clinical and paraclinical evolution*

Datum	Clinical state	Event	Endometrial thickness at TVUS	Sear test	Pathology
1992, Oct.	TN2N0M0 breast cancer	Tumorectomy with axillary dissection			
1993, May		Tamoxifen, 40 mg a day			
1993, Nov.	Asymptomatic	Reducing Tam. to 20 mg daily	7 mm	Smear test normal	
1994, May	Asymptomatic		6 mm		
1994, Nov.	Asymptomatic		6 mm	Rare histiocytes	
1995, Oct.	Asymptomatic			Rare histiocytes	
1996, Dec.	Asymptomatic		4 mm	Smear test normal	
1997, Oct.	Asymptomatic			Presence of normal endometrial cells and histiocytes. Biopsy recommended	
1997, Nov.		Biopsy. Stop Tamoxifen	4.5 mm		Atrophic endometrium
1998, May	Asymptomatic		3 mm	Normal	
1998, Nov.	Asymptomatic		3 mm	Atypical glandular endocervical cells. Cytobrush: Abnormal endometrial cells. Currettage recommended	
1998, Dec.	Asymptomatic	Curettage			Endometrial adenocarcinoma
1999, Jan.	Asymptomatic	Hysterectomy + annexectomy			Endometrial adenocarcinoma stage IVB grade III

monitoring is far from proven. Moreover, the best way to monitor those women is a controversial issue, and various surveillance strategies have been proposed [9, 12-14, 18-23]. If surveillance is performed, the current trend is to recommend low-invasive monitoring schemes for asymptomatic women [21, 24]. Within the strategies using transvaginal ultrasonography as a first-line triage, different cut-off points for endometrial thickness have been proposed ranging from 4 mm [18] to 9 mm [19]. In our institution, we use a cut-off point of 8 mm. Lowering the cut-off point would result in an unacceptably high rate of false positive cases and unnecessary biopsies [11, 12, 15] and so we do not advocate it. The case we report here would have escaped any strategy based on endometrial measurement as the lining was not enlarged.

A yearly Pap smear is part of most follow-up schemes recommended. The presence of atypical or suspicious endometrial cells on the Pap smear calls for an aggressive evaluation which should not end with a negative biopsy [25] since biopsies often provide false negative results. Recommendations in the presence of normal endometrial cells are less drastic. Authors report cancer rates ranging from 1.4% to 20.7%, with a median rate of cancer of 4.5% when normal endometrial cells were found in the Pap smears of post menopausal women [25-28]. In a case-control study of women taking tamoxifen, Abadi *et al.* found that the presence of normal endometrial cells or histiocytes was associated with a higher risk of endometrial cancer [29], but an association with histiocytes has not been reported by others. They therefore recommend that endometrial biopsy or curettage be performed after a smear containing such cells. In the case we describe, biopsy under hysteroscopic control was performed after the Pap smear revealed normal endometrial cells, but the biopsy appeared to be normal. Probably a very focalised cancer can escape this type of probe. Should endometrial resection have been performed at this time? Maybe a future review of all cases of cancer with atrophic endometrium under tamoxifen could help make the guidelines involving cytology results more precise.

Most endometrial cancers associated with tamoxifen are low stage cancers. Fisher reports that in a series of 24 endometrial cancers which developed under tamoxifen, 21 (88%) were FIGO stage I and 18 (78%) of the 23 gradable cases were of good to moderate histologic grade [4]. Barakat *et al.*, in a retrospective review of 73 patients with a history of breast cancer who subsequently developed uterine cancer, found 74% of FIGO stage I or II in patients under tamoxifen, and the same distribution in the group not receiving tamoxifen [30]. In contrast, Magriples *et al.* found 67% of poor stage or poor prognosis cases in a series of 15 patients with uterine cancer which developed under tamoxifen [31], but these data have not been confirmed by any other study. The case we report was a stage IVB grade 3 endometrioïd carcinoma, which is quite uncommon for a tamoxifen-associated cancer. Such a late stage is particularly surprising in the context of an active surveillance strategy, since cancer cases are then expected to be found at an earlier stage.

Conclusion

TVUS can fail to detect cancers if the endometrial lining is not enlarged. The presence of normal endometrial cells on a Pap smear in a woman under tamoxifen can be the only sign associated with an endometrial cancer and should be carefully evaluated.

References

[1] Early Breast Cancer Trialists' Collaborative Group: "Tamoxifen for early breast cancer: an overview of the randomised trials". *Lancet*, 1998, *351*, 1451.

[2] Fornander T., Rutqvist L. E., Cedermark B., Glas U., Mattsson A., Silfversward C. *et al.*: "Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers". *Lancet*, 1989, *1 (8630)*, 117.

[3] Andersson M., Storm H. H., Mouridsen H. T.: "Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer". *J. Natl. Cancer Inst.*, 1991, *83 (14)*, 1013.

[4] Fisher B., Costantino J. P., Redmond C. K., Fisher E. R., Wicherham D. L., Cronin W. M.: "Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14". *J. Natl. Cancer Inst.*, 1994, *86 (7)*, 527.

[5] Cohen I., Rosen D. J., Shapira J., Cordoba M., Gilboa S., Altaras M. M. *et al.*: "Endometrial changes with tamoxifen: comparison between tamoxifen-treated and nontreated asymptomatic, postmenopausal breast cancer patients". *Gynecol. Oncol.*, 1994, *52 (2)*, 185.

[6] Lahti E., Blanco G., Kauppila A., Apaja-Sarkkinen M., Taskinen P. J., Laatikainen T.: "Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen". *Obstet. Gynecol.*, 1993, *81 (5)*, 660.

[7] Kedar R. P., Bourne T. H., Powles T. J., Collins W. P., Ashley S. E., Cosgrove D. O. *et al.*: "Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial". *Lancet*, 1994, *343 (8909)*, 1318.

[8] Neven P., De Muylder X., Van Belle Y., Vanderick G., De Muylder E.: "Hysteroscopic follow-up during tamoxifen treatment". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1990, *35 (2-3)*, 235.

[9] Suh-Burgmann E. J., Goodman A.: "Surveillance for endometrial cancer in women receiving tamoxifen". *Ann. Intern. Med.*, 1999, *131 (2)*, 127.

[10] Seoud M., Shamseddine A., Khalil A., Salem Z., Saghir N., Bikhazi K. *et al.*: "Tamoxifen and endometrial pathologies: a prospective study". *Gynecol. Oncol.*, 1999, *75 (1)*, 15.

[11] Barakat R. R.: "The effect of tamoxifen on the endometrium". *Oncology (Huntingt)*, 1995, *9 (2)*, 129.

[12] Barakat R. R.: "Benign and hyperplastic endometrial changes associated with tamoxifen use". *Oncology (Huntingt)*, 1997, *11 (2 Suppl. 1)*, 35.

[13] ACGO committee opinion: "Tamoxifen and endometrial cancer". No. 169, February 1996, Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists". *Int. J. Gynaecol. Obstet.*, 1996, *53 (2)*, 197.

[14] Neven P., De Muylder X.: "Gynaecology. Hormonal interventions and cancer risk". *Lancet*, 1995, *346 Suppl.*, 8.

[15] Look K.: "The Barakat article reviewed". *Oncology*, 1995, *9 (2)*, 139.

[16] Berek J., Hacker N.: "Practical Gynecologic Oncology". Baltimore: Williams and Wilkin, 1988.

[17] Cardosi R. J., Fiorica J. V.: "Surveillance of the endometrium in tamoxifen treated women". *Curr. Opin. Obstet. Gynecol.*, 2000, *12 (1)*, 27.

[18] Berliere M., Charles A., Galant C., Donnez J.: "Uterine side effects of tamoxifen: a need for systematic pretreatment screening". *Obstet. Gynecol.*, 1998, *91 (1)*, 40.

[19] Franchi M., Ghezzi F., Donadello N., Zanaboni F., Beretta P., Bolis P.: "Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease". *Obstet. Gynecol.*, 1999, *93 (6)*, 1004.

[20] NCI Advisors: "Resume trials, add endometrial sampling". *Cancer Lett.*, 1994, *20*, 3.
[21] Neven P., Vergote I.: "Should tamoxifen users be screened for endometrial lesions? *Lancet*, 1998, *351 (9097)*, 155.
[22] Neven P.: "Tamoxifen: the need for a monitoring protocol". *The Breast*, 1996, *5*, 330.
[23] Assikis V. J., Jordan V. C.: "Gynecologic effects of tamoxifen and the association with endometrial carcinoma". *Int. J. Gynaecol. Obstet.*, 1995, *49 (3)*, 241.
[24] Vosse M., Renard F., Coibion M., Neven P., Nogaret J. M., Hertens D.: "Endometrial disorders in 406 breast cancer patients on tamoxifen: advocating for a low aggressive monitoring". *Eur. J. Obstet. Gynecol. Reprod. Biol.* (in press), 2001.
[25] Yancey M., Magelssen D., Demaurez A., Lee R. B.: "Classification of endometrial cells on cervical cytology". *Obstet. Gynecol.*, 1990, *76 (6)*, 1000.
[26] Ng A. B., Regan J. W., Hawliczek S., Wentz B. W.: "Significance of endometrial cells in the detection of endometrial carcinoma and its precursors". *Acta Cytol.*, 1974, *18 (5)*, 356.
[27] Gondos B., King E. B.: "Significance of endometrial cells in cervicovaginal smears". *Ann. Clin. Lab. Sci.*, 1977, *7 (6)*, 486.
[28] Zucker P. K., Kasdon E. J., Feldstein M. L.: "The validity of Pap smear parameters as predictors of endometrial pathology in menopausal women". *Cancer*, 1985, *56 (9)*, 2256.
[29] Abadi M. A., Barakat R. R., Saigo P. E.: "Effects of tamoxifen on cervicovaginal smears from patients with breast cancer". *Acta Cytol.*, 2000, *44 (2)*, 141.
[30] Barakat R. R., Wong G., Curtin J. P., Vlamis V., Hoskins W. J.: "Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features". *Gynecol. Oncol.*, 1994, *55 (2)*, 164.
[31] Magriples U., Naftolin F., Schwartz P. E., Carcangiu M. L.: "High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients". *J. Clin. Oncol.*, 1993, *11 (3)*, 485.

Address reprint request to:
R. FRANÇOISE, M.D.
Data Centre, Jules Bordet Institute
125 Boulevard de Waterloo
1000 Brussels (Belgium)