Uterine sarcoma associated with tamoxifen use: Case report

M. Martin-Loeches[1], J. Rius[1], R. M. Orti[2]

[1]Department of Gynaecology. "Marina Alta" University Hospital, Alicante
[2]Department of Preventive Medicine. University Hospital Clínic, Valencia (Spain)

Summary

A case of müllerian adenosarcoma with sarcomatous overgrowth in a postmenopausal 66-year-old female patient after adjuvant tamoxifen treatment for breast carcinoma is described.

The patient was asymptomatic and the neoplasm was detected by pelvic sonography. The diagnosis was based on the histological findings after curettage and complementary total hysterectomy with bilateral salpingo-oophorectomy.

The association of tamoxifen use and development of mesenchymal neoplasms is discussed.

Key words: Uterine adenosarcoma; Breast cancer; Tamoxifen; Uterine sarcoma.

Introduction

Over the last 20 years, tamoxifen has become an important component of treatment for both early and advanced hormone receptor-positive breast cancer [1-3]. Recent reports have suggested that tamoxifen has an estrogenic property and may be implicated in the development of endometrial carcinomas, a risk that seems to increase the longer the drug is administered. It is the well known "paradoxical effect" on the female genital tract [1, 2].

It has been unclear whether the incidence of these malignancies is increased in women taking tamoxifen [2, 4]. Concern has been raised about long-term tamoxifen use and the subsequent occurrence of endometrial adenocarcinoma with high-risk histologic subtypes including poorly differentiated patterns and uterine sarcomas [1, 2, 5].

The mechanism for this increased risk is thought to be the estrogen agonist activity of tamoxifen on the uterus, which is similar to the mechanism for increased incidence of uterine cancer in women who take unopposed estrogen as hormone replacement therapy [2, 6].

We discuss the role of tamoxifen on the malignant stromal proliferation of the endometrium and present a case of adenosarcoma with sarcomatous overgrowth in a woman receiving antiestrogen therapy for breast cancer with tamoxifen. Our aim was to further evaluate the possible association of tamoxifen use and an increased risk of uterine sarcoma.

Case report

A 66-year-old nulliparous woman underwent right quadrantectomy and right axillary lymphadenectomy for breast cancer, clinical Stage I. The tumor was invasive ductal comedocarcinoma. The pathological stage was pT1, pN0 and pM0. The surgical treatment was followed by regional radiotherapy and hormonotherapy with tamoxifen therapy with 20 mg daily. After two months of tamoxifen therapy endometrial thickness was determined by ultrasound to be 13 mm and two months later the endometrial thickness was 18 mm. The diagnosis was made by curettage under general anesthesia, and the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy that resulted in a well differenciated FIGO Stage Ia müllerian polypoid adenosarcoma. Vascular or myometrial invasion was not seen.

Discussion

The gynecologic side-effects of tamoxifen are diverse and reflect the complexity of its mechanism of action, with agonistic and antagonistic effects on various tissues. Despite its side-effects, the benefits of tamoxifen in controlling breast cancer or prevention of its relapse are still without debate [2, 4, 7].

The data suggest an association with endometrial cancer [8], but prolonged (> 5 years) tamoxifen treatment may represent a causative factor in the development of this highly lethal disease. Close follow-up of the patients is warranted [3, 9, 10].

There are many reports of sarcomas in patients under tamoxifen use [1, 2, 6 ,8, 10]. Carvalho *et al.* [6] described six cases of uterine adenosarcomas associated with tamoxifen therapy. Considering the rarity of these tumors, it seems that the association of tamoxifen therapy with mesenchymal neoplasm is higher than expected [2, 3, 6].

The spectrum of pathological findings in patients treated with tamoxifen suggests that the drug promotes endometrial growth and that endometrial polyps may be an important intermediate step in endometrial carcinogenesis [8].

We propose close monitoring of patients taking tamoxifen with gynecologic examination plus imaging by means of transvaginal ultrasonography [1]and prompt evaluation of any uterine bleeding or pelvic complaint [8], because many cases was asymptomatic and detected by pelvic sonography [1].

Revised manuscript accepted for publication August 20, 2002

Further studies will be required to establish if there is a relationship between long term tamoxifen exposure and highly aggressive types of cancer of the uterine corpus exhibiting adverse histologic features such as uterine sarcomas [1].

In conclusion, the exact mechanism regarding the role of tamoxifen in the development of epithelial and mesenchymal neoplasms remains unclear, but there is no doubt that all cases of endometrial thickening must be investigated in tamoxifen users [6].

References

[1] Le Bouedec G., Auvray H., Cure H. *et al.:* "Uterine sarcoma in patients receiving tamoxifen therapy. Apropos of 2 cases". *Rev. Med. Inter.*, 2001, *22,* 881.

[2] Wickerham D. L., Fisher B., Wolmark N. *et al.*: "Association of tamoxifen and uterine sarcoma". *J. Clin. Oncol.*, 2002, *20,* 2758.

[3] Barakat R. R.: "Tamoxifen and the endometrium". *Cancer Treat. Res.*, 1998, *94,* 195.

[4] Ismail S. M.: "Pathology of endometrium treated with tamoxifen". *J. Clin. Pathol.*, 1994, *47,* 827.

[5] Liao J. B., Lin J. Y.: "Estrogen receptor expression in an endometrial stromal sarcoma after tamoxifen therapy". *Eur. J. Gynaecol. Oncol.,* 2001, *22,* 417.

[6] Carvalho F. M., Carvalho J. P., Motta E. V., Souen J.: "Müllerian adenosarcoma of the uterus with sarcomatous overgrowth following tamoxifen treatment for breast cancer". *Rev. Hosp. Clin. Fac. Med. Sao Paulo*, 2000, *55*, 17.

[7] Mourits M. J., De Vries E. G., Willemse P. H., Ten Hoor K. A., Hollema H., Van der Zee A. G.: "Tamoxifen treatment and gynecologic side effects: a review". *Anticancer Res.*, 2000, *20,* 2015.

[8] Seoud M. A., Johnson J., Weed J. C. Jr.: "Gynecologic tumors in tamoxifen-treated women with breast cancer". *Obstet. Gynecol.*, 1993, *82,* 165.

[9] Fotiou S., Hatjieleftheriou G., Kyrousis G., Kokka F., Apostolikas N.: "Long-term tamoxifen treatment: a possible aetiological factor in the development of uterine carcinosarcoma: two case-reports and review of the literature". *Anticancer Res.,* 2000, *20*, 2015.

[10] Olah K. S.: "Uterine carcinosarcoma in association with tamoxifen therapy". *Br. J. Obstet. Gynaecol.*, 1997, *104,* 1420.

Address reprint requests to:
M. MARTÍN-LOECHES DE LA LASTRA, M.D.
Calle Abú-Zeyán, 8-1°-2ª
03700 Denia, Alicante (Spain)