Expression of estrogen receptors α and β in two uterine mesenchymal tumors after prolonged tamoxifen therapy. Report of two cases

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Summary

Introduction: Tamoxifen therapy is associated with an increased risk of endometrial carcinoma, and possibly uterine sarcomas. Little is known about hormone receptor expression in mesenchymal tumors of the uterus after tamoxifen therapy.

Cases: The cases of two patients with uterine mesenchymal tumors after prolonged tamoxifen therapy due to breast cancer are presented. The expression of estrogen receptors alpha (ERα) and beta (ERβ) and progesterone receptors (PR) was studied immunohistochemically in both cases. Both tumors were negative for ERα and positive for ERβ. In the first case the tumor was negative for PR, while in the second only 20% of nuclei were PR-positive.

Conclusions: Consistent with previous studies, uterine mesenchymal tumors after tamoxifen therapy do not express ERα. The results of the present report provide for the first time evidence that tamoxifen might exert a stimulatory effect on the uterus, at least during tumor progression, through ERβ but not through ERα.

Key words: Tamoxifen; Uterine sarcoma; Mesenchymal tumors; Estrogen receptors.

Introduction

Currently tamoxifen is the endocrine treatment of choice in all stages of hormone receptor-positive breast cancer in both pre- and postmenopausal women [1, 2]. Furthermore, clinical trials have demonstrated the utility of tamoxifen in ductal carcinoma in situ (DCIS) and in risk reduction for women at high risk for developing breast cancer [2-4]. Clinical trials have consistently shown that women with breast cancer taking tamoxifen are at increased risk for developing endometrial cancer [2, 5]. Recently an increasing number of reported cases led to a new warning issued by the FDA advising doctors that tamoxifen may also increase the risk of uterine sarcoma [6-8]. The warning was aimed at women with DCIS and those at high risk for breast cancer, but it does not apply to women who have already had breast cancer since the benefits from the drug far outweigh its risks [6, 7].

Thus far, very little is known about hormone receptor expression in uterine sarcomas and generally uterine mesenchymal tumors after tamoxifen therapy [9, 10]. We present two additional cases of uterine mesenchymal tumors after tamoxifen therapy for breast cancer, with an immunohistochemical study on the expression of estrogen receptors (ER) alpha and beta as well as progesterone receptors (PR).

Case 1

A 63-year-old, white woman, gravida 0, para 0 presented with metrorrhagia. She had a history of modified radical mastectomy with axillary lymphadenectomy for a tumor of the right breast, ten years earlier, followed by local irradiation and tamoxifen, 20 mg/day, for the following ten years. Pelvic examination and transvaginal ultrasound showed an enlarged uterus. CT-scan of the abdomen confirmed the presence of an enlarged uterus, suggesting a uterine neoplasm. Total abdominal hysterectomy with bilateral salpingo-oophorectomy followed. Microscopic examination showed a carcinosarcoma of the endometrium, FIGO Stage IB. The patient received postoperatively five courses of combination chemotherapy, but refused further treatment. Recent follow-up showed that the patient remains disease-free, five and a half years after hysterectomy.

On gross examination the uterus measured 9 x 5 x 3 cm. On cut sections a polypoid lesion was found protruding from the posterior wall into the uterine cavity and partly infiltrating the myometrium. The lesion measured 4 x 3.5 cm, was soft in consistency and whitish-yellow in color. Histology showed carcinomatous and sarcomatous elements intermingling with each other (Figure 1). Heterologous elements were not observed. Immunohistochemical stains for ERα (6F11, Novocastra laboratories Ltd, UK) and PR (PgR636, DAKO Corporation USA) did not show positivity in the neoplastic cells. Immunohistochemical stain for ERβ (385P, Biogenex, San Ramon CA) showed positivity in about 50% of the nuclei in carcinomatous areas and 75% in sarcomatous areas (Figure 2). Dark, bizarre nuclei in the latter were usually negative.

Case 2

A 57-year-old, white woman, gravida 2, para 2 presented with metrorrhagia. She had a history of modified radical mastectomy with axillary lymphadenectomy for a tumor of the left breast ten years earlier, followed by local irradiation, chemotherapy and tamoxifen for the following ten years (30 mg/day for the first 5 years and 20 mg/day for the following 5 years). On pelvic examination and transvaginal ultrasound the

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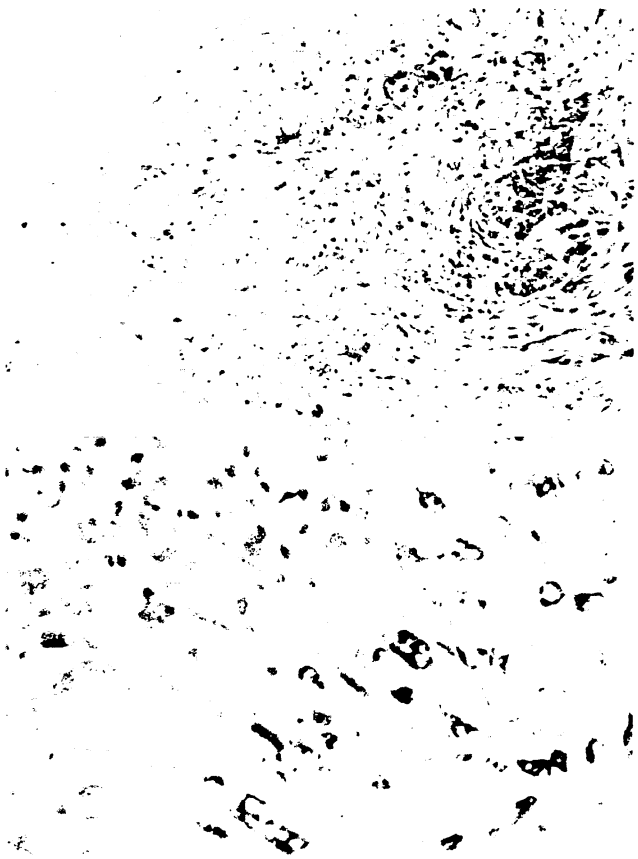

Fig. 2

ig. 3

Fig. 4

Figure 1. — Case 1 - Carcinosarcoma of the endometrium (H&E, original magnification x 100).
Figure 2. — Case 1 - Immunohistochemical positivity for ERβ (original magnification x 400).
Figure 3. — Case 2 - Smooth muscle tumor of unknown malignant potential (H&E, original magnification x 400).
Figure 4. — Case 2 - Immunohistochemical positivity for ERβ (original magnification x 200).

uterus was enlarged. Total abdominal hysterectomy with bilateral salpingo-oophorectomy followed. Microscopic examination showed a smooth muscle tumor of unknown malignant potential and a small focus of well-differentiated adenocarcinoma. The patient received postoperatively six courses of combination chemotherapy. Four years after hysterectomy there were no signs of recurrence.

On gross examination the uterus measured 12 x 10 x 5 cm. Two intramural tumors were found on sectioning, the larger in the lower uterine segment measuring 2.5 cm in its largest dimension and protruding on the outer surface. On cut sections the above tumor showed soft consistency and reddish-brown color in places. Histology revealed a smooth muscle tumor with necrotic areas showing characteristics of coagulative tumor cell necrosis and increased mitoses in the surrounding cells (up to 8 per 10 high power fields). There was mild atypia. The neoplasm was diagnosed as a smooth muscle tumor of unknown malignant potential, with a comment concerning the low malignant group described by Bell *et al.* [11] (Figure 3). The endometrium was postmenopausal in places, with areas of complex atypical hyperplasia and a small focus of well-differentiated adenocarcinoma. The second intramural tumor was a leiomyoma. Immunohistochemistry showed negativity for ERα, and positivity of 20% of the nuclei for PR and 60% of the nuclei for ERβ in the smooth muscle tumor of unknown malignant potential (Figure 4).

Discussion

Tamoxifen administration in breast cancer patients and for breast cancer chemoprevention is based on its antiestrogenic properties, although the drug may also act by non-estrogen-receptor-related mechanisms [1]. The response of estrogen-sensitive tissues to tamoxifen varies among species and sites of action. This tissue-specific action brings about the paradox of tamoxifen as an anticancer drug in breast cancer and as a carcinogenic agent in the uterus, and the contradictory effects on the female genital tract as a whole [1].

The first case report connecting tamoxifen with endometrial cancer was published in 1985 [12], and since then an increased risk of developing endometrial cancer in women taking tamoxifen has been a consistent finding in clinical trials [2]. The first case reports of uterine sarcoma after tamoxifen [13, 14] were published in 1993, followed by an increasing number of reported cases [9, 10, 15-20]. Since 1978, at least 43 cases of uterine sarcoma in the United States and 116 in other countries have been reported in women taking tamoxifen [6]. Pure sarcomas and malignant mixed epithelial-mesenchymal tumors make up approximately 10% of the total of uterine malignancies in patients receiving tamoxifen [2].

They occur in 0.17 per 1,000 patients a year taking this drug, compared to 0.01 to 0.02 cases per 1,000 women not taking the drug [7]. Histologically, about three quarters of these cases are malignant mixed mullerian tumors (MMMTs) [2]. There are no reports in the literature concerning smooth muscle tumors of low or unknown malignant potential (LMP or STUMP) after tamoxifen use. The median duration of exposure to tamoxifen in the reported cases was five years. In the present report exposure to tamoxifen was prolonged, lasting ten years in both cases.

The molecular mechanisms by which tamoxifen exerts its action on the uterus are not fully understood and several mechanisms have been proposed. It has been suggested that, in women treated with tamoxifen, endometrial cancer is related to an estrogen agonist effect that promotes cell proliferation rather than to conversion of the drug to metabolites leading to nuclear DNA damage [21]. The identification of estrogen receptor beta (ERβ) in 1996 [22], almost ten years after the cloning of ERα, has added more complexity to our understanding of estrogen and SERM signalling. Both types of ERs bind tamoxifen with comparable affinity but a lack of agonistic effect of tamoxifen on ERβ has been reported [23, 24].

ER and PR expression in uterine sarcomas after tamoxifen therapy has been analyzed in two previous studies. Bergman *et al.* [9] in a nationwide case control study in the Netherlands found that uterine tumors that developed after tamoxifen therapy and were negative for ER(α) and PR were more often MMMTs or endometrial sarcomas. However, the authors did not give more details, particularly concerning the receptor status of individual tumors. Liao and Lin [10] analyzed immunohistochemically paraffin sections of an endometrial stromal sarcoma after tamoxifen therapy for the expression of ER(α) and PR. Consistently with the previous study this tumor was negative for ER(α), but in contrast it was positive for PR. The authors concluded that the absence of ER(α) expression suggests that endometrial stromal sarcomas are not necessarily caused by the estrogenic properties of tamoxifen. Reduced ER(α) expression has been also observed immunohistochemically in endometrial hyperplasias and polyps after tamoxifen treatment by two groups of investigators [25, 26], leading to the hypothesis that tamoxifen might lead to down-regulation of ER [26]. In the present report, both tumors were negative for both hormone receptors and only the tumor in case 2 was in part (20%) positive for PR. These findings, together with those of the aforementioned studies could support the view that tamoxifen might lead to sarcoma formation through an ERα- and possibly PR-independent pathway. However, the lack of ERα- and PR-expression could be due to a positive selection of cells not expressing ERα and/or PR. In other words, ERα and PR did not seem to promote tumor progression in these cases, however their involvement in the genesis of these neoplasms cannot be totally ruled out.

To the best of our knowledge analysis of the expression of ERβ in mesenchymal tumors after tamoxifen treatment has never been done so far. Our findings that both tumors in the present report were ERβ-positive and at the same time ERα-negative suggest that tamoxifen might exert its stimulatory effect on the uterus via an ERβ-dependent pathway. It can be postulated that ERβ are at least involved in tumor progression in such cases, while no evidence exists to directly support their possible contribution in tumorigenesis. These hypotheses should be tested in future studies in a considerable number of cases, probably by including not only patients under tamoxifen therapy but also patients not receiving the medication.

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