Large endometrial polyp with sarcomatous stromal components following long-term tamoxifen treatment for breast cancer: a case report and review of the literature

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Summary

Tamoxifen is commonly used in the management of patients with breast cancer because of its anti-oestrogenic effects to the breasts. However, tamoxifen acts as an oestrogen agonist on the endometrium increasing the incidence of endometrial polyps, hyperplasia and cancer. In addition, it may be possible that tamoxifen increases the occurrence of uterine body tumours. We describe a rare case of a large endometrial polyp with sarcomatous stromal components in a 73-year-old breast cancer patient treated daily with 20 mg of tamoxifen for four years. The glands of the polyp were lined by benign appearing epithelium. The polyp was twisted and protruded from a dilated cervix at the entrance of the vagina. The patient was treated by removal of the polyp and dilatation and curretage. A postoperative computed tomography scan showed many focal hypodense lesions in the hepatic lobes with a well-defined profile suggestive of metastatic disease and the patient was referred for combined chemotherapy. In conclusion, a case of a mesenchymal malignant neoplasm arising in the uterus of a breast cancer patient treated with tamoxifen is reported and its clinical, histological and immunohistochemical features are discussed. Also, the international literature is reviewed.

Key words: Uterus; Polyp; Tamoxifen; Sarcoma; Mesenchymal tumours.

Introduction

Tamoxifen is a non-steroid anti-oestrogen which is commonly used in the management of patients with breast cancer [1]. Tamoxifen was introduced for clinical trials in Europe in 1971 and was approved by the Food and Drug Administration in the United States in 1977 for the treatment of advanced breast cancer. Since that time, the list of indications has expanded and includes use in selected pre- and postmenopausal women for node-negative, node-positive and metastatic breast cancers [2, 3]. It has also been shown that a combination of tamoxifen and chemotherapy reduces the risk of recurrences of breast cancer in the ipsilateral breast and development of cancer in the contralateral breast [4, 5]. Moreover, tamoxifen can be used for the prevention of breast cancer in high-risk women [6].

The acute side-effects associated with tamoxifen use include hot flashes, vaginal discharge, oedema, nausea and depression. However, only 4% of patients discontinue the drug because of these adverse effects [7]. Although tamoxifen has an anti-oestrogenic effect on the breast, it may act as an oestrogen agonist on the endometrium. In 1985, Killackey *et al.,* first suggested a possible link between tamoxifen use and the development of endometrial carcinoma in three patients [8]. Since then, there have been numerous reports confirming this association [9]. Long-term tamoxifen treatment has also been reported to increase the occurrence of endometrial polyps and hyperplasia [10]. In addition, tamoxifen use may increase the occurrence of uterine body tumours, such as stromal sarcomas, leiomyosarcomas and malignant mixed epithelial/non-epithelial tumours [9, 11-13].

In this report we document an extremely rare case of an endometrial megalopolyp with sarcomatous stromal components and benign epithelium in a postmenopausal breast cancer patient receiving long-time tamoxifen treatment. We present the clinical, pathological and immunohistochemical features of this rare case and review the international literature.

Case Report

The patient was a 73-year-old woman with an obstetrical history of two normal deliveries. She had a gynaecological history of regular menses occurring every 28 days and she had been postmenopausal since her mid-50s. She measured 160 cm in height, weighed 70 kg, and had a seven-month history of atrial fibrillation since her admission to our hospital. There was no history of diabetes mellitus or hypertension. Past medical history was significant for a 25 x 25 mm infiltrating invasive ductal, grade 2, carcinoma of the left breast at the age of 69 years. She subsequently underwent modified radical mastectomy and lymphadenectomy. Nine of the 12 totally removed axillary lymph nodes were involved with metastatic carcinoma; three of the invasive nodes were removed from level II and six from level III. Subsequently, the patient was started on *peros* tamoxifen treatment at a dose of 20 mg daily. She was not treated with other hormonal therapy, chemotherapy or radiotherapy. Follow-up of the endometrium with transvaginal ultrasonography, hysteroscopy or dilatation and curettage was not performed.

Revised manuscript accepted for publication March 25, 2003

Four years later, the patient experienced heavy vaginal bleeding for five days and was admitted to the hospital. Gynaecological examination revealed a large mass which prolapsed through the external cervical os and appeared at the entrance of the vagina. The mass was connected to the uterus by a thick stalk and was removed at the operating room under general anaesthesia rotating it around its axis.

A postoperative CT scan of the upper and lower abdomen revealed many focal hypodense lesions in the hepatic lobes with a well-defined profile suggestive of metastatic disease. The patient was referred for six cycles of adjuvant-combined chemotherapy of taxol and carboplatin.

Pathological study

Gross pathologic examination revealed that the tumour was a dark red mass measuring 9.5 x 9 x 5 cm (Figure 1). Its cut surface was mainly dark red and solid, while in a grayish-white area, measuring 5 x 3 x 1 cm, several small cysts were present.

Microscopic examination demonstrated an endometrial polyp in the form of a glandular component intimately admixed with sarcomatous stromal elements. The polyp showed extensive vascular congestion, haemorrhagic infiltration, necrosis and elements of epigenic infection because of torsion (Figure 2). The endometrial glands were hyperplastic and cystically dilated without any atypia, and some presented with secretory elements. The stroma in some peripheral areas was hypocellular, whereas around the glands it was mainly cellular and slightly fasciculated with elongated cells. Focally, trabeculae of sarcomatous stromal cells with vesicular nuclei and atypical mitotic figures were found (Figure 3). The nonpolypoid endometrium was unremarkable.

An immunohistochemical study revealed strong and diffuse positivity for α-smooth muscle actin in the elongated stromal cells of the endometrial polyp. These cells showed negative immunostaining for desmin and vimentin. The sarcomatous stromal elements showed a positive reaction for myoglobulin, but a negative reaction for α-smooth muscle actin. Oestrogen and progesterone receptors showed a moderate positive reaction in both epithelial and sarcomatous stromal areas. The marker Ki-67 was expressed at a rate of 10%. The case was determined to be Müllerian adenosarcoma of the uterus with sex cord-like elements.

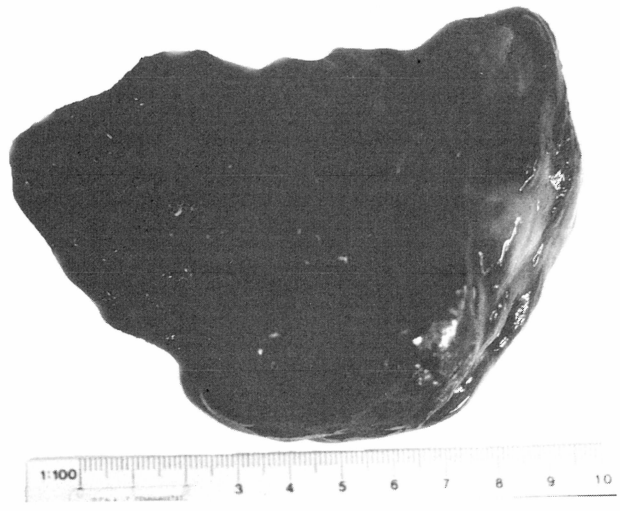

Figure 1. — Large endometrial polyp, measuring 9.5 x 9 x 5 cm after long-term tamoxifen treatment in a 73-year-old breast cancer patient.

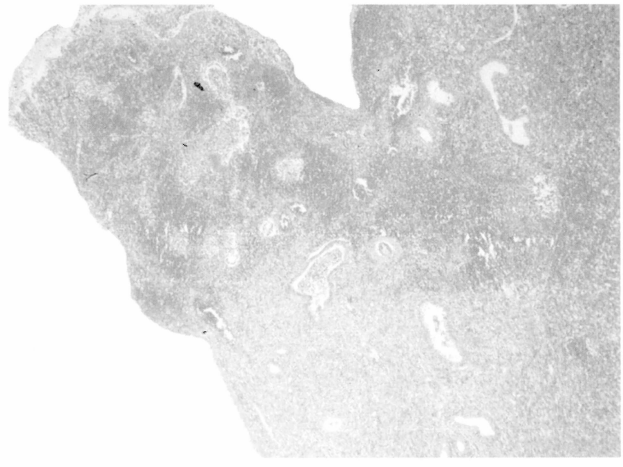

Figure 2. — Endometrial polyp showing extensive vascular congestion, haemorrhagic infiltration, necrosis and elements of epigenic infection secondary to its torsion (Haematoxylin and eosin, x30).

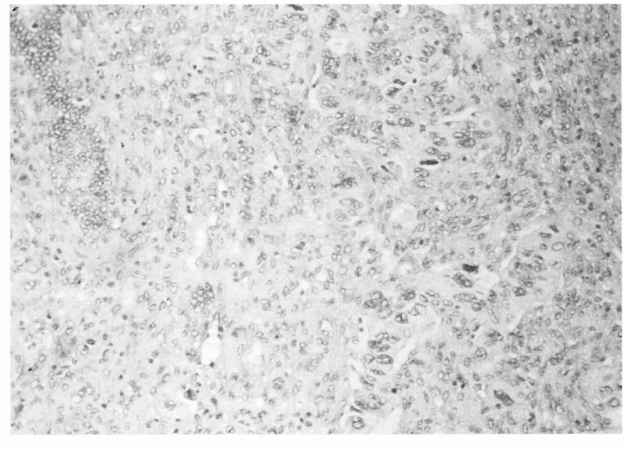

Figure 3. — Malignant mesenchymal elements of the tumour (Haematoxylin and eosin, x125).

Discussion

Uterine sarcomas account for 3-5% of all uterine malignancies [14] and are classified in three main histologic subgroups in order of decreasing incidence: malignant mixed epithelial/non-epithelial tumours, leiomyosarcomas, and endometrial stromal sarcomas [9, 12]. Variants of malignant mixed epithelial/non-epithelial tumours are malignant mixed Müllerian tumours (or carcinosarcomas), adenosarcomas and adenofibromas [9]. Müllerian adenosarcomas were first described by Clement and Scully in 1974 [15] and represent only 8% of all uterine sarcomas [11, 16]. These tumours are biphasic and contain benign or atypical epithelial, and a malignant stromal component [17, 18]. They present as polypoid masses usually arising from the endometrium and can invade the subajacent myometrium [17]. Cases have also been reported arising from the myometrium,

cervix, ovaries, fallopian tubes, pelvis and peritoneum [19, 20-22]. Most adenosarcomas are of low malignant potential [17].

An endometrial polyp is generally called a focal circumscribed overgrowth of the mucosa, usually the basal portion, which protrudes into the uterine cavity. It is thought that such polyps are formed either from a focal hypersensitivity to oestrogen or a local insensitivity to progesterone. Polyps do not occur before the menarche but during the fifth decade [23]. Endometrial polyps are rarely associated with neoplasmatic changes, with only a 0.5% chance of cancer present within the polyp [24]. The association of tamoxifen with endocervical and endometrial polyps has been demonstrated by several studies. Lahti *et al.,* found that endocervical polyps were twice as common and endometrial polyps three times as common in a tamoxifen group than in a control group [25].

The risk of developing endometrial cancer before the age of 85 is 1.1% [26]. Women with carcinoma of the breast have a higher risk than expected of developing subsequent uterine carcinoma. The risk is estimated to be 1.72 times the risk of developing endometrial cancer [27], is age-dependent and is approximately 1.0 in women younger than 50 years and closer to 2.4 in women 70 years or older [27]. Because tamoxifen has oestrogen-like effects on the endometrium, it might represent a risk factor for endometrial carcinoma [28]. Several studies have indicated an association between tamoxifen treatment and endometrial carcinoma [9]. An overview of all the randomized tamoxifen trials in 1998 showed that the incidence of endometrial cancer was approximately double in trials of tamoxifen lasting one or two years and approximately quadrupled in trials of five years duration [1]. Moreover, tamoxifen has been associated with occurrence of uterine sarcomas [9]. Several cases after tamoxifen therapy have been reported in the international literature. Most of these sarcomas are malignant mixed Müllerian tumours, while a few cases of Müllerian adenosarcomas of the uterus, and endometrial stromal sarcomas have been reported as well [29]. In a review of the literature by Arici *et al.,* 13 Müllerian adenocarcinoma cases following tamoxifen therapy were reported [18]. Ten patients had received tamoxifen for periods of five months to four years, one patient for five years and one for eight years. In one patient the duration of tamoxifen use was not reported. The clinical and pathological features of these cases were similar to previously reported Müllerian adenosarcoma cases, except for their association with tamoxifen therapy [18]. In our case, the patient was treated with low doses of tamoxifen (20 mg daily) for four years. However, the patient had not undergone annual gynaecological examinations. We should keep in mind the hypothesis that large endometrial polyps may represent an intermediate step in tumour formation [13]. Uterine adenosarcomas may be subject to hormonal influences, since endometrial stromal sarcomas and malignant mixed Müllerian tumours have been reported to be oestrogen and/or progesterone receptor-positive [11, 29]. In our case the immunohistochemical expression of oestrogen and progesterone receptors in the sarcomatous stromal elements suggests a hormonally dependent development of this malignancy.

Regarding the action of tamoxifen on the endometrium, it seems that tamoxifen binds to the oestrogen receptors in the oestrogen-binding domain (HBD), which is located in the functional domain E of the oestrogen receptor and forms dimmers of activated oestrogen receptors. These dimmers bind to the specialized oestrogen response elements (EREs) of the DNA in the endometrial cells. This binding allows the activation of the function of the region AF-1 of the oestrogen receptor, which mediates activation of the transcription (oestrogen-independent transcriptional activating function, AF-1). The mitogen function of tamoxifen in the endometrium is perhaps explained by the activation of proto-oncogenes exclusively by the function of the region AF-1. In contrast, in the breast the expression of proto-oncogenes depends on the activation of the function of the region AF-2, which is only activated by oestrogens (oestrogen-inducible transcriptional activating function, AF-2). The over-expression of proto-oncogenes caused by tamoxifen may be responsible for carcinogenesis in the endometrium [9, 30, 31]. Varras *et al.,* suggested an accessional mechanism of the cancerous action of tamoxifen on the endometrium by the induction of mutation in codon 12 of the K-*ras* oncogene [32].

In conclusion, we have presented the clinical and pathological findings in a 73-year-old patient, who developed a large uterine polyp with sarcomatous stromal elements and benign endometrial epithelium, following low dose tamoxifen therapy after four years. The case was diagnosed as Müllerian adenosarcoma of the uterus. Considering the rarity of Müllerian adenosarcomas, it seems that the association of tamoxifen therapy with mesenchymal neoplasms is higher than expected.

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