# MÜLLERIAN ADENOSARCOMA OF THE UTERUS WITH SARCOMATOUS OVERGROWTH FOLLOWING TAMOXIFEN TREATMENT FOR BREAST CANCER

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SUMMARY: Müllerian adenosarcoma with sarcomatous overgrowth presented by a 52-year-old female patient after adjuvant tamoxifen treatment for breast carcinoma is described. The diagnosis was made on histological basis after curettage and complementary total hysterectomy with bilateral salpingo-oophorectomy. The immunohistochemical study showed high expression of estrogen receptors in the epithelial component of the lesion and irregularly positive findings in the stroma. The proliferative activity evaluated by Ki-67 immunoexpression was higher in the stroma than the epithelium. Some of the stromal cells showed rhabdomyoblastic differentiation. The association of tamoxifen use and development of mesenchymal neoplasms is discussed.

DESCRIPTORS: **Uterine adenosarcoma. Breast cancer. Tamoxifen. Uterine sarcoma.**

Adenosarcomas are characterized as tumors containing benign or atypical epithelial and malignant stromal components. They present as polypoid masses arising from the endometrium and can invade the subjacent myometrium. Most adenosarcomas are tumors of low malignant potential. Recurrence occurs in approximately 24% of cases and is related to deep myometrial invasion[5]. A variant from the usual pattern with a sarcomatous overgrowth has been described by Clement[6]. This variant is an overgrowth of the adenosarcoma by a pure sarcoma with consequent higher recurrence rate, metastases, and fatal outcome[6].

Of the 100 cases described by Clement and Scully, 5 had a history of estrogen use; 1 had a history of maternal usage of a hormone of unknown type during the first trimester of pregnancy, and 1had a diagnosis of Stein-Leventhal syndrome[5]. Two patients of this series had carcinoma of the breast that was treated 5 and 2.5 years earlier[5]. Recently, Mourits et al. (1998) described a case of a 71-year-old patient who developed a uterine adenosarcoma after two years of adjuvant tamoxifen treatment for breast cancer[13].

We discuss the role of tamoxifen on the benign and 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.

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## CASE REPORT

A 52–year-old multiparous woman underwent left mastectomy and right quadrantectomy for bilateral breast cancer, clinical stage II. Both tumors were invasive ductal carcinoma. The pathological stages were pT2, pN2 and pT2, pN1biii, respectively at left and right. The surgical treatment was followed by 6 cycles of taxol and adriamycin and regional radiotherapy at both breasts. Five months after the surgery she began tamoxifen therapy with 20 mg daily. After 6 months of tamoxifen therapy, endometrial thickness was determined by ultrasound to be 5.8 mm. Five months later the endometrial thickness was 11 mm, and 1 year later it was 27 mm. The diagnosis was done by curettage under general anesthesia, and the patient under-

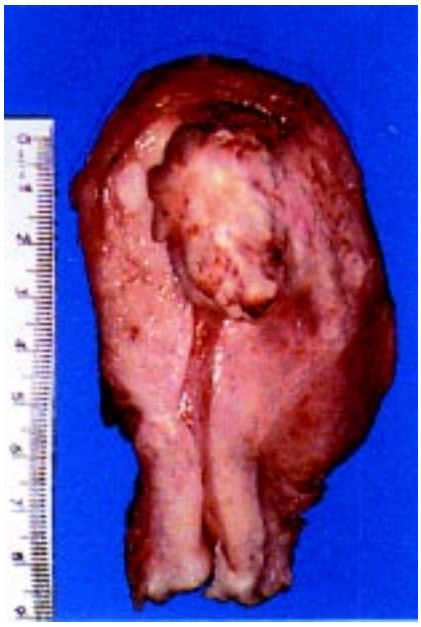

**Figure 1** - Product of total hysterectomy with polypoid lesion in the endometrium.

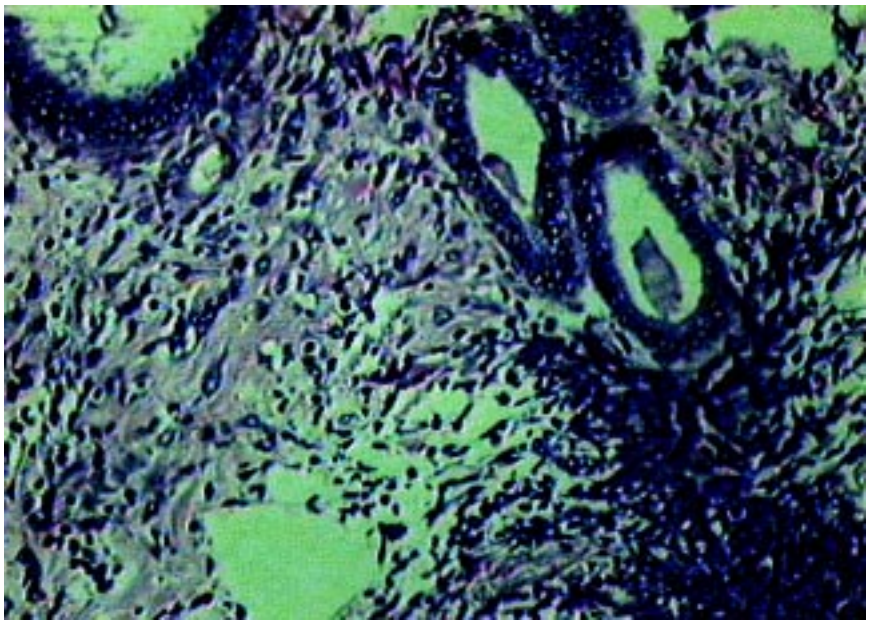

**Figure 2** - Histological aspect of the endometrial lesion, showing the epithelial and stromal component. Note the hypercellular area near the gland (hematoxylin-eosin; 100X).

went total abdominal hysterectomy with bilateral salpingo-ooforectomy.

PATHOLOGICAL STUDY

The uterus was enlarged, weighed 230 g and measured 9.5 X 6.1 X 5.2 cm. The uterine cavity measured 8.5 cm in length and had an endometrial polypoid lesion measuring 4.0 cm that was partially necrotic with signs of superficial myometrial invasion. (Fig. 1). The microscopic examination showed a biphasic neoplasm with glands of endometrioid pattern and a cellular stromal component that tended to coalesce into more densely hypercellular cuffs around the epithelial component (Fig. 2). The stromal cells were spindle-shaped or pleomorphic and had rhabdoid areas (Fig. 3). The mitotic count was 6 per 10 high power field (HPF). Areas of prominent stromal component accounted for 40% of the tumor. There were foci of stromal fibrosis and hemorrhage without necrosis. Vascular invasion was not seen. There were areas of superficial myometrial invasion.

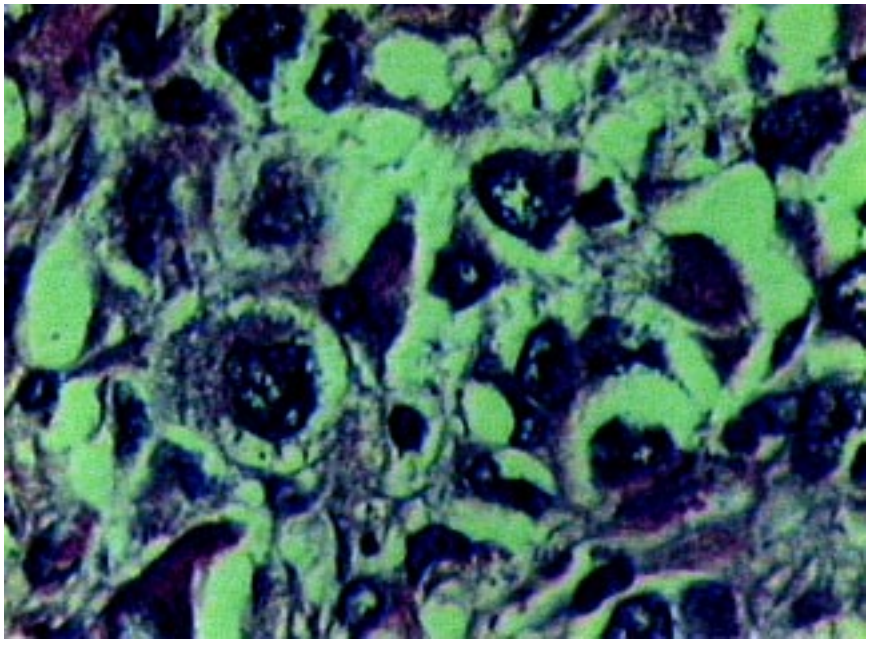

**Figure 3** - Area of neoplastic stroma with pleomorphic and rhabdoid cells (hematoxylin-eosin; 400X).

The immunohistochemical study was carried out to identify estrogen receptor (ER), proliferative activity, and rhabdomyoblastic differentiation with the monoclonal antibodies 1D5 (Dako), MIB-1 (Immunotech) and desmin DE-R-11 (Dako), respectively. Eighty percent of epithelial cells were positive for estrogen receptors, and stromal cells were irregularly positive for estrogen receptors. Twenty percent of stromal cells and 5% of epithelial cells were positive for MIB1, indicating that the proliferative activity was higher in the stroma. The more pleomorphic areas were positive for

desmin, indicating muscular differentiation.

## DISCUSSION

Breast cancer treatment with tamoxifen has been associated with the development of hyperplasia and carcinomas of the endometrium[17]. However, the most common finding has been uterine polyps[8,10,18,19]. Fotiu et al.[11] have studied the histopathologic features of 50 curettage specimens from patients under tamoxifen treatment and experiencing abnormal bleeding; 44% had cervical and endometrial polyps. A clinical study of 245 cases has found an association of endometrial polyps and tamoxifen in 8% of patients with breast cancer.[15] Exacoustos et al.[10] have observed thicker endometrium in patients receiving tamoxifen compared to controls. In that study, 23 cases of pathological endometrium out of 38 cases were observed: 19 polyps and 4 hyperplasia[10].

Tesoro et al.[19] found 24 cases of abnormal endometrium in a group of 80 postmenopausal women treated with tamoxifen for breast cancer: 13 polyps, 5 hyperplasia, 3 tubal metaplasia, 2 carcinomas, and 1 breast carcinoma metastatic to endometrium.[19] Polypoid structures, morphologically similar to endometrial polyps, were observed even in endometriotic foci in patient under tamoxifen treatment[16]. The occurrence of polyps is increased in tamoxifen-treated postmenopausal women compared with untreated patients, but this alteration is not observed in premenopausal tamoxifen-treated[12]. On the other hand, some workers have found lower levels of estrogen and progesterone receptors in endometrium of postmenopausal tamoxifen-treated patients than in control groups composed of healthy women with and without estrogen replacement therapy[7]. In our study, positivity for ER was lower in the stromal component of the lesion compared with the epithelium and inversely proportional to the proliferative activity. This finding was the same as that noticed by others [13] and can be explained by a loss of expression of steroid receptors due to neoplastic transformation. Considering that the epithelial component is not neoplastic yet, it expresses high levels of receptor. This finding can explain the development of hyperplastic lesions and carcinomas in some endometria. Some groups have found carcinoma arising within tamoxifen-associated endometrial polyps[14].

There are many reports of sarcomas in patients under tamoxifen use[1,2,4,18]. Clement et al.[4] described 6 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.

The proliferative effect of tamoxifen in endometrium seems to be related to an effect primarily on stromal cells and perhaps on vascular structures. The polyps, so frequently associated with tamoxifen use, are proliferation with an important stromal-vascular component. Zhao et al.[20] have shown that endometria of women receiving tamoxifen express adrenomedullin, a growth factor for endotelial cells, postulating that induction of this angiogenic factor is part of the mechanism by which tamoxifen results in endometrial hyperplasia. Bhargava et al.[3], using in vitro model, have found an increase in the proliferative activity due to tamoxifen in the endometrial stromal cells over the controls. Decensi et al.[9] compared endometria of tamoxifen-treated breast cancer patients and controls and have observed an antiproliferative effect of tamoxifen on the epithelium and a growth-promoting effect on the stroma, suggesting that the endometrial proliferation is mediated by the stromal component.

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.


## RESUMO

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CARVALHO F M e col. – Adenossarcoma Mülleriano com componente sarcomatoso predominante, após tratamento adjuvante do câncer de mama com tamoxifeno. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55** (1):17-20, 2000.

É descrito o caso de uma paciente do sexo feminino, 52 anos, com adenossarcoma Mülleriano com componente sarcomatoso predominante, que se apresentou após tratamento adjuvante com tamoxifeno para câncer de mama. O diagnóstico foi feito em bases histológicas após curetagem uterina e histerectomia total complementar com anexectomia bilateral. O estudo imuno-histoquímico mostrou alta expressão de receptores de estrogênio no componente epitelial da lesão e positividade irregular no

estroma. A atividade proliferativa avaliada através da imunoexpressão do Ki-67 foi maior no estroma do que no epitélio. Algumas células estromais mostraram diferenciação rabdomioblástica. A associação entre uso de tamoxifeno e desenvolvimento de neoplasias mesenquimais é discutida.

DESCRITORES: **Adenossarcoma uterino. Câncer de mama. Tamoxifen. Sarcoma uterino.**

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