A case of synchronous relapse of breast cancer and uterine müllerian adenosarcoma post tamoxifen in a premenopausal woman

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Summary

Purpose & Methods: We report a case of a 42-year-old multigravida, premenopausal woman with breast carcinoma, who presented after four years of use of adjuvant tamoxifen with synchronous liver, bone, and lung metastasis of breast cancer with müllerian adenosarcoma. *Results:* Immunohistochemical stains on the uterine tumor for estrogen and progesterone receptors showed positivity for both epithelial and stromal cells, actin, and desmin while the proliferative index (MIB-1) showed positivity for stromal cells only. The patient underwent a hysterectomy followed by palliative chemotherapy. She died 14 months after her relapse because of progressive disease (cerebral, bone, liver and lung metastases). *Conclusion:* Our case is the only one reported in the literature with synchronous relapse of breast adenocarcinoma and a Müllerian adenosarcoma. Moreover, it is one of the rare cases occurring in a premenopausal woman since all except two cases were postmenopausal.

Key words: Premenopausal, Müllerian adenosarcoma, Relapse, Tamoxifen, Uterine.

Introduction

Tamoxifen, a non-steroidal antiestrogen, is used at all stages of breast cancer in pre- and postmenopausal women as an adjuvant or palliative therapy, as well as a prophylactic drug for women identified at high risk of hormone-dependent breast cancer [1]. Several studies have shown its association with an increased incidence of endometrial cancer [2] which was explained by the fact that tamoxifen shows various responses from different estrogen sensitive tissues. Effectively, it is anti-carcinogenic in the breast, while it is carcinogenic in the endometrium [3].

Uterine müllerian adenosarcoma is increasingly being reported as a side-effect of tamoxifen adjuvant therapy [4-12]. This tumor has been documented to be associated with long-term estrogen exposure.

Case Report

A 42-year-old multigravida premenopausal woman was diagnosed as having a breast cancer, ductal type, Stage IIA T2 N(2+/27) M0, with positive estrogen and progesterone receptors, a high proliferative index (MIB1), and a score of 3 for cerb-B2 using the immunohistochemical method. At that time she underwent a modified radical mastectomy followed by six cycles of chemotherapy (5FU, doxorubicin, and cyclophosphamide) and loco-regional irradiation. Tamoxifen was then initiated in an adjuvant setting at a dose of 20 mg. No other medications were used.

Forty-five months after the initial diagnosis, the patient presented with bone pain. The work-up revealed the presence of generalized relapse with liver, bone, and lung metastases. The appearance of vaginal bleeding led to a gynecological exam which revealed a protruding polypoid lesion and enlarged uterus. The patient underwent an ultrasonography that confirmed the enlargement of the uterus with an increase in the thickness of the endometrium; therefore, a dilatation and curettage was performed. The uterus weighed 760 g with a polypoid mass arising from the endometrium measuring 10.5 cm in the maximum dimension; no myometrial invasion was noted. The cut surface was soft with cystic areas containing mucinous material (Figure 1).

The diagnosis of tamoxifen-associated adenosarcoma in this case was readily apparent and the patient underwent hysterectomy.

Immunohistochemistry showed estrogen and progesterone receptor positivity in both epithelial and stromal cells (30%), c-erbB2 (Her 2 neu) negativity, smooth muscle actin and desmin positivity for stromal cells, and a high positive proliferative index (MIB-1).

Discussion

This report documents another case of the rare uterine tumor Müllerian adenosarcoma associated with tamoxifen therapy. In 1974, Clement and Scully first introduced the term müllerian adenosarcoma to designate a very rare uterine malignancy composed of benign or mildly atypical glands admixed with a sarcomatous, usually low-grade, stromal component [4]. The literature reviewed revealed around 15 cases [4-12] and 12 cases from seven papers were compared clinically and histologically with our case (summarized in Table 1). Our case is one of the rare cases occurring in a premenopausal woman since this tumor occurs mainly in postmenopausal women and all except two cases were postmenopausal [4]. Additionally, our case is the only case reported in the literature

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Table 1. — *Summary of the clinical and histological features of reported and reviewed uterine Mullerian.*

Authors	Age	Presentation	Gross	Mito-sis 10 HPF	Heterologus element	T-duration	Breast tumor state	LN	Rx	ER	PR	Myometrial invasion
Blockage *et al*. 1992	53	bleeding abdominal fullness	Polypoid in adenoma	47	none	13 months	PD	4/10	Chemo Rad	+	+	Minimal
Clement *et al*. 1996 †	48-76	bleeding (3) polyp (1) No sx* (1)	Polypoid (5) NA (6)	< 3 (4) 6 (1) 9 (1)	none	6, 2, 3, 4, 4 and 4 years	NA	NA	NA	NA	NA	Upper 1/3 (2 cases)
Carvalho *et al*. 2000	52	bleeding abdominal pain	Polypoid	6	none	1 year	Bilateral Stage II	N2	Chemo Rad	NA	NA	superficial
Arici *et al*. 2000	58	bleeding	Polypoid	5	none	5 years	Grade I	12/19	Chemo Rad	+	NA	–
Jessop & Roberts 2000	68	bleeding	Polypoid	10	none	31 months	NA	NA		NA	NA	–
Mhawech *et al*. 2000	71	bleeding	Polypoid	29	none	38 months	NA	NA	Rad	NA	NA	superficial
Martin-Loeches *et al*. 2000	66	Endometrial thickening	Polypoid	NA	none	4 months	Comedo Stage I	N0	Rad	NA	NA	–
Case report presented	42	bleeding	Polypoid	40	Mature cartilage	4 years	Stage: T2	N2	Chemo Rad	+	+	–

† This paper presented 6 cases. *sx: symptoms; NA: not available; HPF: high power field; chemo: chemotherapy; Rad: radiotherapy.

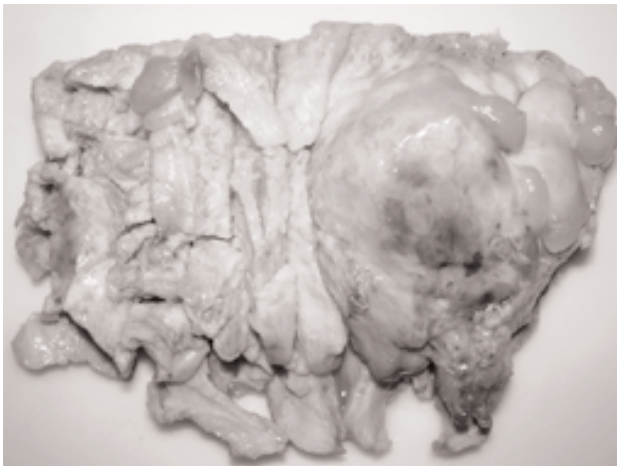

Figure 1. — Tumor occupying the endometrial cavity showing small cysts containing mucinous material.

with synchronous relapse of the breast adenocarcinoma and a müllerian adenosarcoma.

All but three of the reported cases presented with vaginal bleeding: one with a polyp protruding from the vaginal vault [3], another after a regular gynecological check-up, where endometrial thickening was noted [11] and one asymptomatic case [3]. The lymph node status varied from no metastasis to 12 out of 29 (2 out of 27 axillary lymph nodes in our case). As in our case, all patients received adjuvant chemotherapy and radiotherapy, except one case where only radiotherapy was employed [9]. The duration of 20 mg adjuvant tamoxifen administration varied from one case to another ranging from four months to five years. The shorter period of appearance of Müllerian sarcoma was observed in the reported case presented by Martin-Loeches [11] where the patient was found to have increased endometrial thickness two months after tamoxifen initiation and the biopsy revealed the diagnosis of uterine Müllerian sarcoma. In our case, the patient was recommended to have a repeated gynecological follow-up after tamoxifen intake but she did not show up and was lost to follow-up.

In all reported cases smooth muscle actin was positive, indicating the muscular origin of these tumor cells. Desmin was variable but vimentin was positive. Estrogen and progesterone receptors were also positive. In the cases reported in the literature all except one were negative [9] suggesting that the loss of these receptors is due to their proliferative activity [5].

The cases of uterine müllerian adenosarcoma associated with tamoxifen, as reported from the papers reviewed, revealed similar histological features to those occurring without tamoxifen intake history. The prognosis of women with uterine sarcomas or adenocarcinomas who had taken tamoxifen was not any poorer than that of women not exposed to tamoxifen; in fact for both histologic subgroups, the probabilities of survival were greater among women treated with tamoxifen (median follow-up, 85 months) [12].

In conclusion, the benefit to risk ratio of tamoxifen in the treatment of breast cancer patients is definitely high. Even though adenosarcoma represents a rare endometrial malignancy and its association with tamoxifen therapy makes its occurrence even rarer, pathologists should keep in mind this differential diagnosis whenever examining endometrial material.

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