Malignant mixed mullerian tumor in two patients receiving tamoxifen therapy

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ABSTRACT

Patients with breast cancer exhibit an increased risk in developing neoplasms of other organs. In the case of the endometrium, the increased risk might be due to tamoxifen adjuvant therapy. We present two cases of homologous malignant mixed mullerian tumor (MMMT) of the uterine in two women, 77-year-old and 76-year-old, respectively, after tamoxifen treatment for postmenopausal breast cancer with positive estrogen receptors. The findings for two patients were studied and compared with similar ones discussed in the relevant literature.

Key words: breast cancer, uterine, tamoxifen

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Received: 20.06.2011
Accepted: 24.06.2011
Progress in Health Sciences
Vol. 1(1) · 2011 · pp 167 - 170.

INTRODUCTION

The term *Mixed Mullerian Tumor* describes a group of tumors arising from the undifferentiated mullerian stroma and consisting of both epithelial and non-epithelian elements [1, 2]. MMMT is a relatively rare uterine neoplasm [3, 4] that account for <5% of uterine malignancies [4] and 3-5% of all uterine malignancies [5].

They are seen practically always in postmenopausal patients, although exceptions occur. They are composed of malignant epithelial and stromal components. MMMTs occur in the uterus, ovaries, fallopian tubes and vagina, in descending order of frequency [6]. Depending on the histology of the mensenchymal components a distinction is made between homologous and heterologous MMMT [7]. In the heterologous variant, mesenchymal elements are present, such as striated muscle, cartilage, bone and adipose tissue, not normally found at this site [6]. The distinction between homologous and heterologous MMMT is prognostically insignificant [7].

When a postmenopausal woman with a cervical mass is admitted to the gynecology clinic, the physician should keep in mind that the mass might be a carcinosarcoma [8]. Mesenchymal tumors, including MMMTs, endometrial stromal sarcomas, mullerian adenosarcoma, leiomyosarcomas and uterine pleomorphic rhabdomyosarcomas, have been more recently described with tamoxifen use [3,9] and have a poor prognosis.

In this paper, we report two cases of MMMT in patients with breast cancer, who had received tamoxifen.

CASE 1

Clinical history

A 76-years old patient was admitted to the authors department, due to postmenopausal bleeding of several month durations. Because of that, she had performed a dilatation and diagnostic curettage. She had her menarche at the age of 12 and was menopausal for the past 31 years, at the age of 45. She had 2 normal deliveries and 5 abortions. She did not receive estrogen replacement.

Pathology

The histological investigation revealed an extensive adenocarcinoma of the endometrium, with moderate differentiation of papillary and endometrioid type. The stroma had a sarcomatous appearance, dense cellular structure, and contained spindle-like cells. Thus, a mullerian mixed tumor of homologous type of the uterine corpus was diagnosed.

The patient received a percutaneous irradiation with 46 Gy. Three months following surgery, local recurrence of the tumor was observed, and she died, due to rapid dissemination of the tumor.

Subsequent clinical history

According to the family medical report, the father of the patient died because of stomach cancer. Her relevant medical history until the age of 65 was tonsillectomy appendectomy and thyroidectomy. Ten years prior to her referral, she underwent a right partial mastectomy, because of infiltrating lobular breast carcinoma in tumor stage pT1, pN0, M0, G2, ER+++, PR--. She received irradiation with Co^{60} to the right breast and an adjuvant therapy with 20mg tamoxifen daily for 5 years. One year ago she also commenced chemotherapy, because of "mass" in her right breast, with abnormal limits and diffuse pain of the bones. The protocol of combination chemotherapy composed of Eye 1gr (or C19 in one cycle), NoV 20mg, F750mg, NoV 1(5) and Aredia 60mg. Because of complications of severe anemia and neutropenia, she received amp Eprex 1000 and amp Tardyferon (1×2). During the 9 cycles of chemotherapy, she experienced fracture of her left arm. Following this, she continued with Aredia 60mg (1×1), Eye 1g, NoV 20mg, 5Fu 750mg, NoV1(5), Or4 and End19.

CASE 2

Clinical history

A 77-years old multiparous woman sought medical attention, because of postmenopausal bleeding from her vagina. She had her menarche at the age of 13 and became menopausal at 45. She was not placed on any hormone replacement regiment. She had 6 normal deliveries and 3 abortions. The patient underwent a dilatation and curretage.

Pathology

Histological examination of the endometrial curettage showed a total occupation of a malignant tumor with the characteristics of homologous MMMTs. Microscopically, the lesion was composed of an extensive biphasic tumor, consisting of solid epithelial formations. The stroma had a dense cellular structure and contained spindle-like partially fibroblastic parts. Immunohistochemically, a smooth muscle actin immunoperoxidase stained was positive in the cytoplasm of many of the neoplastic mesenchymal

cells. A few months later, she underwent a second endometrial biopsy**.** Microscopically, extensive infiltrations of fibrolipomatous tissues of elements of adenocarcinoma moderately differentiated were observed. The stroma presented fibroblastic reaction and were accompanied by psammoma bodies.

A bilateral oophorectomy was performed, with the left ovary measured 2,2×1,5×1 cm and the right ovary measured 2,5×1,3×0,8 cm. In addition, a part of the omentum measured 8×5×2 cm and a part of the fallopian tube with length 3,5 cm was removed. Microscopically, the left ovary presented atrophic changes. The right ovary presented atrophic changes and focal infiltrations of serous papillary adenocarcinoma, of moderate differentiation. In the stroma, psammoma bodies were present. The part of the omentum presented focal hyperplasia of mesothelial cells, with a focus of metastatic serous papillary adenocarcinoma of the ovary. The tube was normal. The patient died 8 months after the first operation, because of cardiopathy.

Subsequent clinical history

In the relevant medical history of the patient, appendectomy and cardiopathy were reported. At the age of 68, the patient noticed a mass in her right breast. A biopsy revealed an infiltrating ductal and lobular breast carcinoma, and she underwent a right total mastectomy and axillary node dissection. The tumor stage was pT2, pN0/33, M0, G2, ER++, PR-. She received radiotherapy (4000 rad) to the right breast with Co^{137} and an adjuvant therapy with tamoxifen 10mg (1×3) for 5 years.

DISCUSSION

The only documented etiologic factor in 10% to 25% of MMMT is prior pelvic radiation therapy, which is often administered for benign uterine bleeding that began 5 to 25 years earlier. An increased incidence of uterine sarcoma has been associated with tamoxifen in the treatment of breast cancer. Subsequently, increases have also been noted when tamoxifen was given to prevent breast cancer in women at increased risk—a possible result of the estrogenic effect of tamoxifen on the uterus [10-12].

Tamoxifen is a synthetic nonsteroid triphenyl antiestrogen drug, structurally similar to the ethylstibestriol. Tamoxifen, an estrogen receptor agonist and antagonist, has both therapeutic and preventive role in breast cancer [13]. This drug, however, has been found to cause activation of estrogen receptors, leading to estrogenic effects on the postmenopausal endometrium [3].

The low incidence of uterine sarcomas makes it difficult to establish a relationship with tamoxifen. Nevertheless, looking at the literature data, 20 mg/day of tamoxifen over 1 year could be enough to develop uterine sarcoma; the sarcoma appears mainly during the first 8 years and seems to behave more aggressively [14].

Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial lesions [15, 16].

In consequence, early detection of tamoxifen-related uterine sarcoma is required for orderly gynecological examination in patients having a of tamoxifen usage for previous breast cancer [17].

There is a very strong association between the tamoxifen treatment and the occurrence of MMMTs of the uterine corpus. However, the distinct possibility of such a rare association in the development of these neoplasms should be kept in mind at the routine follow-up of patients, or in those suffering from abnormal uterine bleeding.

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