Carcinosarcoma Arising in Uterine Didelphys after Tamoxifen Therapy for Breast Cancer: A Case Report

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The occurrence of uterine cancer in breast cancer patients who received tamoxifen treatment, is well described. To our knowledge, an association between uterine anomaly and uterine carcinosarcoma in these patients had not been reported. We present a case of uterine carcinosarcoma occurring in uterine didelphys of a 72-year-old breast cancer patient, who had been treated with tamoxifen for 5 years. The patient presented with large pelvic mass. The uterine anomaly was not recognized preoperatively. The patient died of disease 5 months after diagnosis. Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial lesions.

Keywords: Uterine carcinosarcoma, Uterine didelphys, Tamoxifen, Breast cancer

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Case Report

A 72-year-old woman was a known case of breast cancer diagnosed in October 2000. She had T3N1M0 invasive ductal carcinoma of the right breast and was treated by simple mastectomy with axillary lymphadenectomy. She also received adjuvant chemotherapy that consisted of cyclophosphamide, methotrexate, and 5-fluorouracil. In March 2001, after six cycles of chemotherapy, she was given oral tamoxifen at 20 mg daily continuously without any endometrial monitoring.

In May 2006, the patient experienced abnormal vaginal discharge and pelvic pain. A physical examination revealed an enlarged pelvic mass above the umbilicus. A pelvic examination showed a single vagina with an “enlarged” cervix. A large pelvic mass was palpated, but could not be separately identified as a uterus or adnexa. Both parametria were free. An abdominal ultrasonography showed a large mass on the left side of the pelvis and absence of the right kidney. A Pap smear revealed neoplastic glandular epithelium that was also detected by cervical biopsy and was interpreted as adenocarcinoma in situ. Other
pre-operative investigations were normal. The clinical diagnosis was uterine or ovarian cancer with cervical involvement.

The patient underwent an exploratory laparotomy, which discovered 100 ml of serosanguineous ascites and an enlarged uterus showing two bulbous horns of the corpus, with the left being the larger. A simple hysterectomy with bilateral salpingooophorectomy was performed. The cervix had two separate ostia. Observation on opening the uterus showed the left horn filled with large intracavitary exophytic masses (Fig. 1). The right horn showed diffuse thickening of the endometrium with numerous small cysts. The mucosa of both endocervical canals was not grossly remarkable, except for a communicating defect connecting each one. Additional partial omentectomy was done. The pelvic and paraaortic nodes were not sampled, due to intraoperative cardiac arrhythmia.

The histologic diagnosis was carcinosarcoma that arose in the left horn of uterine didelphys. The carcinomatous component was composed of poorly-differentiated endometrioid and serous adenocarcinoma, whereas the sarcomatous component was predominantly rhabdomyosarcoma (Fig. 2). The adenocarcinomatous component invaded to almost

Fig. 1  (A, B) Didelphys uterus with malformation diagram. The endocervical canal of each horn is separated from each other with a small communication. The endometrial cavity is filled with large masses of solid tissue with marked necrosis. The right horn shows thickened endometrial lining with cystic appearance (obliteration of the isthmus is also present)

Fig. 2  Carcinosarcoma. Malignant glandular epithelium overlaying the malignant stromal component is composed of pleomorphic stromal cells with eosinophilic cytoplasm. Inset: rhabdomyoblastic cell with cross striation
the entire myometrial thickness, with lymphovascular space invasion and direct invasion to the cervical wall. The other cervix was not involved. The residual non-neoplastic endometrium in the left horn and the endometrial lining of the right horn had a similar appearance characterized by polypoid endometrial thickening with fibrotic stroma and occasional hyperplastic foci with glandular nuclear atypia. The left adnexa, the omentum, and the ascites cytology were negative for malignancy. The tumor was classified as at least FIGO stage IIIB. The patient denied further adjuvant treatment. Seven weeks later, she developed a local recurrence at the vaginal stump and was given pelvic radiotherapy. The patient died of disease five months after diagnosis.

Discussion

Tamoxifen, a nonsteroidal antiestrogen agent, is commonly used as an adjunctive therapy for women with breast cancer. It reduces local relapses, increases overall and disease-free survival, and decreases the development of tumor in the contralateral breast(11). However, a disadvantage of tamoxifen therapy in these patients is an increased risk of endometrial lesions such as endometrial polyps, endometrial hyperplasia, atypical hyperplasia, and uterine cancers—either adenocarcinoma or sarcoma(6).

The incidence of uterine cancers related to tamoxifen therapy is 160 per 100,000 patients per year for endometrial carcinoma(12) and only 0.5 per 100,000 patients per year for uterine sarcoma(13). Carcinosarcoma has traditionally been regarded as a subtype of uterine sarcoma(14). However, recent evidence suggests that this neoplasm may be closely related to endometrial carcinoma and that the sarcomatous component should represent metaplastic transformation or dedifferentiation of the epithelial component(15). The association between tamoxifen exposure and carcinosarcoma has been described mostly as small case series. The patients ranged from 42 to 90 years of age. The interval between the start of tamoxifen treatment and the presentation of uterine carcinosarcoma ranged from 16 to 240 months(7-10). In this report, the patient had been treated with tamoxifen for 63 months prior to the diagnosis of uterine cancer. The association between the presence of uterine malformation and the occurrence of uterine cancer is uncommon. Only a few cases of endometrial cancer arising in patients with mullerian abnormalities have been reported, and, to the authors’ knowledge, none of them was related to tamoxifen exposure(16,17).

Such association is rare. It is difficult to make a definite conclusion and a coincidence may be a possible explanation. In the present case, uterine didelphys was not detected preoperatively. However, the palpation of the other hidden cervix led to an initial impression of cervical enlargement. Even though, the abdominal ultrasonography did not demonstrate the uterine malformation, the finding of a single left kidney serves as a preoperative clue to the presence of mullerian malformation. The incidence of one kidney agenesis associated genital anomalies has been estimated at up to 50%(18). Magnetic resonance imaging (MRI) is a helpful investigation in confirming the presence of uterine didelphys(17).

In the presented patient, carcinosarcoma occurred in one uterine horn within the background of diffuse endometrial changes that were characteristic of tamoxifen-related lesions(19). The mechanism of tamoxifen in the induction of endometrial pathology may be explained by its estrogen agonist activity, which is similar to that in women who developed endometrial cancer after taking unopposed estrogen as hormonal therapy(20). The concentration of tamoxifen metabolites has been demonstrated as higher in the endometrium compared to the serum, and this may be important in the endometrial carcinogenesis(21). Other non-estrogenic effects of tamoxifen, such as damaged DNA, may also be an alternative explanation for, or contribution to, the development of uterine sarcoma(22).

In the presented patient, tamoxifen induced diffuse endometrial thickening with fibrotic stroma in both horns, accompanied by foci of hyperplastic glands with nuclear atypia. The right horn had the most severe atypical changes with progression to malignant neoplasm, which grew within that horn by clonal expansion(21). The left horn had no neoplastic involvement due to anatomical separation from the right one.

Among tamoxifen-exposed patients, who developed subsequent uterine cancers, those with carcinosarcoma presented at a more advanced stage than those with endometrial adenocarcinoma(24). Carcinosarcoma is regarded as a high-grade malignancy with aggressive behavior. The prognosis of women with uterine sarcoma, who were exposed to tamoxifen, was not significantly different to that of those without tamoxifen exposure(25).

The ACOG committee suggested that postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial lesions and should receive regular gynecologic care. Any abnormal
vaginal bleeding, bloody vaginal discharge, staining or leucorrhea should be investigated. It is important that the clinicians involved should be aware of and follow such a suggestion in promoting an early diagnosis of uterine cancer in these patients.

In conclusion, tamoxifen remains a beneficial drug as an adjuvant treatment of breast cancer. On the other hand, this drug should be used with precaution against the development of uterine malignancy. This association can occur in mullerian duct abnormality.

References
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รายงานผู้ป่วยที่เคยได้รับการรักษามะเร็งเต้านมด้วยยา tamoxifen แล้วเกิดมะเร็งเม็ดลูกชนิด carcinosarcoma ในเม็ดลูกที่มีลักษณะปกติแบบ uterine didelphys

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เป็นที่ทราบกันดีว่าผู้ป่วยมะเร็งเต้านมที่ได้รับยา tamoxifen รับประทานต่อเนื่องจะมีความเสี่ยงสูงขึ้นในการเกิดมะเร็งเม็ดลูก ดังจะก่อให้เกิดความเสี่ยงที่จะเกิดภาวะลูกเหล่าที่มีความผิดปกติของเม็ดลูกมาแต่กำเนิด กับการเกิดมะเร็งเม็ดลูกชนิด carcinosarcoma ยังไม่มีรายงานมาก่อน บทความนี้ได้นำเสนอผู้ป่วยรายหนึ่งอายุ 72 ปี ซึ่งเริ่มมีอาการมีก้อนในท้อง และได้รับการรักษาด้วย tamoxifen กินเป็นเวลา 5 ปี มาพบแพทย์ด้วยเรื่องมีก้อนในท้อง และได้รับการรักษาโดยการผ่าตัด และพบมีมะเร็ง uterine carcinosarcoma บริเวณ horn ซึ่งผู้ป่วยไม่เคยทราบมาก่อนว่าน่าจะมีเม็ดลูกชนิด carcinosarcoma ในผู้ป่วยเต้านมด้วยยา tamoxifen ดังนั้นการรักษาควรให้เสริมหลังจากได้รับการรักษาใน 5 เดือน ต่อมา