

Case Report

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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Uterine didelphys is a type of congenital abnormality of the uterus, resulting from a lateral fusion defect of two müllerian ducts. Each duct forms one cervix, one uterine body, and one fallopian tube on each side. It is defined as type III müllerian duct abnormality according to the modified American Fertility Society classification of müllerian duct fusion and resorption abnormalities. The incidence of uterine didelphys is approximately 10% of all müllerian anomalies^(1,2).

Tamoxifen is a synthetic antiestrogen drug that is widely used as an adjunctive therapy for women with estrogen receptor-positive breast cancer⁽³⁻⁵⁾. However, this agent also has modest estrogenic activity on the endometrium. Postmenopausal patients with breast cancer, who have received long term tamoxifen therapy, are more commonly found to have endometrial pathology and uterine cancers compared to those who have not⁽⁶⁾. Approximately 50 cases of uterine carcinosarcoma, developing in breast cancer patients after tamoxifen exposure, have been reported in the English literature, none of which was associated with

a uterine malformation⁽⁷⁻¹⁰⁾. The authors present one such case, in which carcinosarcoma developed in one horn of the didelphys uterus.

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

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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 salpingo-oophorectomy 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

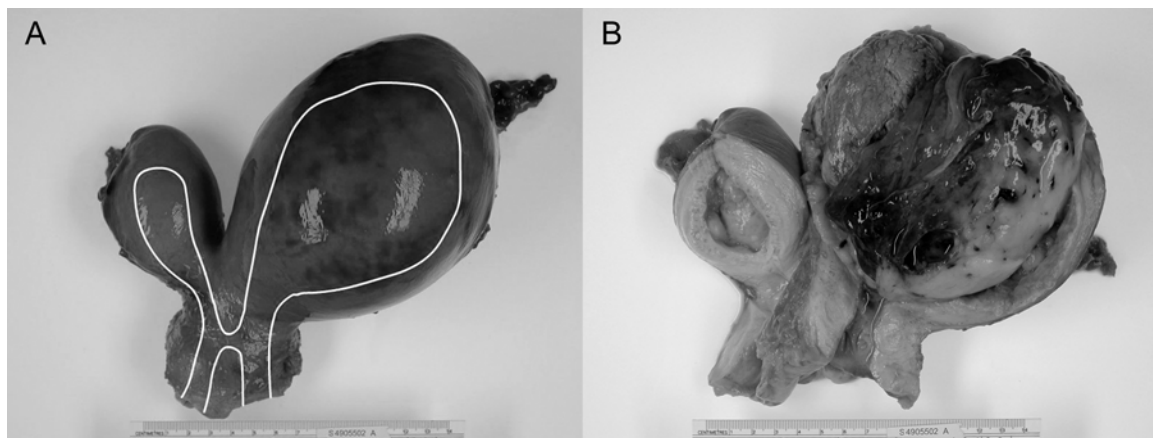


Fig. 1 (A, B) Didelphys uterus with malformation diagram. The endocervical canal of each horn is separated from each other with a small communication. The endometrial cavity is filled with large masses of solid tissue with marked necrosis. The right horn shows thickened endometrial lining with cystic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

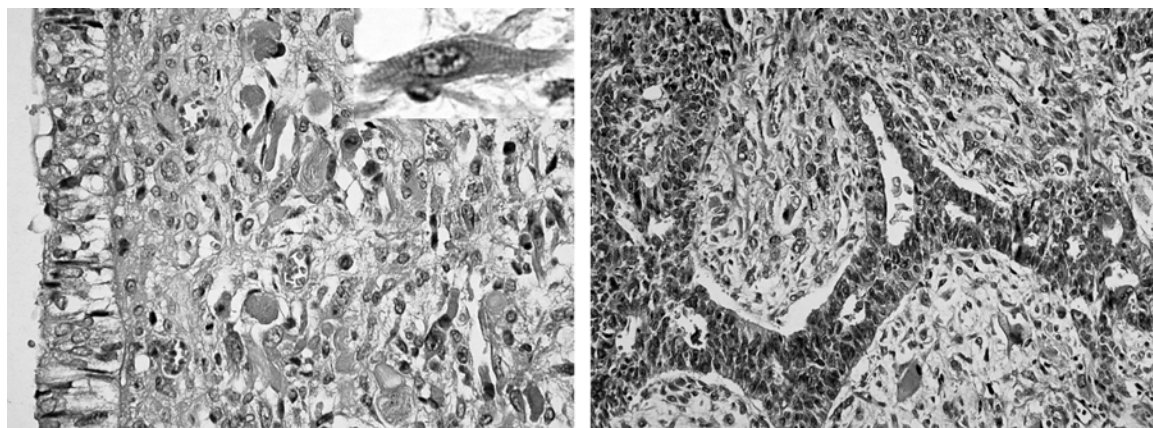


Fig. 2 Carcinosarcoma. Malignant glandular epithelium overlaying the malignant stromal component is composed of pleomorphic stromal cells with eosinophilic cytoplasm. Inset: rhabdomyoblastic cell with cross striation

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 IIB. 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 müllerian 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 müllerian 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⁽²³⁾. 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⁽²⁶⁾. 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

1. Elford KJ, Spence JE. The forgotten female: Pediatric and adolescent gynecological concerns and their reproductive consequences. *J Pediatr Adolesc Gynecol* 2002; 15: 65-77.
2. Molpus KL, Puleo JG, Williams AM, Bernal KL, Remmenga SW. Endometrial adenocarcinoma within a single horn of a didelphic uterus: a report of 2 cases. *J Reprod Med* 2004; 49: 123-5.
3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451-67.
4. Juneja M, Jose R, Kekre AN, Viswanathan F, Seshadri L. Tamoxifen-induced endometrial changes in postmenopausal women with breast carcinoma. *Int J Gynaecol Obstet* 2002; 76: 279-84.
5. Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfversward C, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989; 1: 117-20.
6. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol* 2004; 94: 256-66.
7. Arenas M, Roviroso A, Hernandez V, Ordi J, Jorcano S, Mellado B, et al. Uterine sarcomas in breast cancer patients treated with tamoxifen. *Int J Gynecol Cancer* 2006; 16: 861-5.
8. Kloos I, Delalogue S, Pautier P, Di Palma M, Goupil A, Duvillard P, et al. Tamoxifen-related uterine carcinosarcomas occur under/after prolonged treatment: report of five cases and review of the literature. *Int J Gynecol Cancer* 2002; 12: 496-500.
9. Hubalek M, Ramoni A, Mueller-Holzner E, Marth C. Malignant mixed mesodermal tumor after tamoxifen therapy for breast cancer. *Gynecol Oncol* 2004; 95: 264-6.
10. Yildirim Y, Inal MM, Sancı M, Yildirim YK, Mit T, Polat M, et al. Development of uterine sarcoma after tamoxifen treatment for breast cancer: report of four cases. *Int J Gynecol Cancer* 2005; 15: 1239-42.
11. McCluggage WG, McManus DT, Lioe TF, Hill CM. Uterine carcinosarcoma in association with tamoxifen therapy. *Br J Obstet Gynaecol* 1997; 104: 748-50.
12. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994; 86: 527-37.
13. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002; 346: 1832-3.
14. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer* 1993; 71: 1702-9.
15. Sreenan JJ, Hart WR. Carcinosarcomas of the female genital tract. A pathologic study of 29 metastatic tumors: further evidence for the dominant role of the epithelial component and the conversion theory of histogenesis. *Am J Surg Pathol* 1995; 19: 666-74.
16. Fanfani F, Fagotti A, Restaino G, Guerriero M, Scambia G. Endometrial cancer arising in both horns of didelphys uterus in a Down's syndrome woman. *Gynecol Oncol* 2006; 101: 537-9.
17. Bhalla R, Evans H, Berger L, Crow J, Deheragoda M, Taper Y. A uterus didelphys bicollis, with endometrial cancer in both uteruses. *J Obstet Gynaecol* 2005; 25: 823-5.
18. Thompson DP, Lynn HB. Genital anomalies associated with solitary kidney. *Mayo Clin Proc* 1966; 41: 538-48.
19. Ismail SM. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994; 47: 827-33.
20. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995; 85: 304-13.
21. Giorda G, Franceschi L, Crivellari D, Magri MD, Veronesi A, Scarabelli C, et al. Determination of tamoxifen and its metabolites in the endometrial tissue of long-term treated women. *Eur J Cancer* 2000; 36(Suppl 4): S88-9.
22. Martin EA, Brown K, Gaskell M, AlAzzawi F, Garner RC, Boocock DJ, et al. Tamoxifen DNA damage detected in human endometrium using accelerator mass spectrometry. *Cancer Res* 2003; 63: 8461-5.
23. Nowell PC. The clonal evolution of tumor cell

- populations. Science 1976; 194: 23-8.
24. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371-88.
 25. Bernstein L, Deapen D, Cerhan JR, Schwartz SM, Liff J, McGann-Maloney E, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst 1999; 91: 1654-62.
 26. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006; 107: 1475-8.

รายงานผู้ป่วยที่เคยได้รับการรักษามะเร็งเต้านมด้วยยา tamoxifen แล้วเกิดมะเร็งมดลูกชนิด
carcinosarcoma ในมดลูกที่มีลักษณะผิดปกติแบบ uterine didelphys

ประภาพร สุประเสริฐ, สุรพันธ์ คุณอมรพงศ์

เป็นที่ทราบกันดีว่าผู้ป่วยมะเร็งเต้านมที่ได้รับยา tamoxifen รับประทานต่อเนื่องจะมีความเสี่ยงสูงขึ้นในการเกิดมะเร็งของตัวมดลูก แต่อย่างไรก็ตามความสัมพันธ์ระหว่างผู้ป่วยที่มีความผิดปกติของตัวมดลูกมาแต่กำเนิดกับการเกิดมะเร็งมดลูกชนิด carcinosarcoma ยังไม่มีรายงานมาก่อน บทความนี้ได้นำเสนอผู้ป่วยรายหนึ่งอายุ 72 ปี ซึ่งเป็นมะเร็งเต้านม และได้รับยา tamoxifen กินเป็นเวลา 5 ปี มาพบแพทย์ด้วยเรื่องมีก้อนในท้อง และได้รับการรักษาโดยการผ่าตัด และพบว่า เป็น uterine carcinosarcoma บริเวณ horn ข้างหนึ่งของ uterine didelphys ซึ่งผู้ป่วยไม่เคยทราบมาก่อนว่าตนเองมีมดลูกผิดปกติ ผู้ป่วยเสียชีวิตจากโรคหลังได้รับการวินิจฉัยใน 5 เดือน ต่อมา