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Case Report

Synchronous uterine carcinosarcoma and contralateral breast cancer after tamoxifen therapy: a case report

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Abstract: Uterine carcinosarcoma (malignant mixed Müllerian tumor, MMMT) is a rare aggressive malignant tumor, which demonstrates both malignant epithelial (carcinoma) and mesenchymal (sarcoma) components. Synchronous uterine carcinosarcoma and contralateral breast cancer in patient received tamoxifen treatment had not been reported. We present a case of uterine carcinosarcoma co-occurrenced with contralateral breast cancer in a 56-year-old nulliparous, obese breast cancer patient, who had been treated with tamoxifen for 5 years. The patient presented with palpable pelvic mass and vaginal bleeding. Histopathological evidence revealed that the tumor was comprised of an admixture of malignant epithelial and mesenchymal components. The epithelial component was endometrioid type adenocarcinoma, while sarcomatous component had heterologous elements including fusiform cell sarcoma and a prominent component of cartilage. The infiltrating ductal carcinoma has been diagnosed on her right breast. The patient died of disease 8 months after diagnosis. Postmenopausal patients, with adjuvant tamoxifen treatment for breast cancer, are at increased risk for the development of uterine carcinosarcoma and less benefit for contralateral breast cancer.

Keywords: Uterine carcinosarcoma, contralateral breast cancer, tamoxifen

Introduction

Nulliparity and obesity are associated with increased risks for both breast and uterine cancers [1]. Approximately, 2-11% of women diagnosed with breast cancer will develop contralateral breast cancer [2]. Tamoxifen therapy might reduce risk for contralateral breast cancer [3], including BRCA1 and BRCA2 mutation carriers [4]. However, tamoxifen therapy substantially increases the risk of uterine carcinosarcoma (also known as malignant mixed müllerian tumor), which is a rare aggressive malignancy with an estimated annual incidence of 0.82/100,000 worldwide, and accounts of 2-4% of uterine tumor [5, 6]. Most reported cases of uterine carcinosarcoma occurrenced in patients with unilateral breast cancer, synchronous uterine carcinosarcoma and contralateral breast cancer after tamoxifen therapy has not been described previously.

Case report

A 56-year-old nulliparous, obese female patient (BMI: 28.8) was admitted to Department of Obstetrics and Gynecology, The First Affiliated Hospital of Shantou University Medical College, China with a 3-week history of postmenopausal vaginal bleeding accompanied by low abdominal pain. She went into menopause at age 48-years-old, and had no family history of cancer and prior pelvic radiation therapy. Her medical history was significant for left breast carcinoma requiring a radical mastectomy 7 years ago, and had been taking tamoxifen 20 mg once per day for 5 years as adjuvant endocrine therapy.

On physical examination, there were a palpable pelvic mass prolapsed into the vagina and vaginal discharge noted on vaginal examination. A large (6×7 cm), hard and poorly mobile lump had been observed in the upper outer quadrant

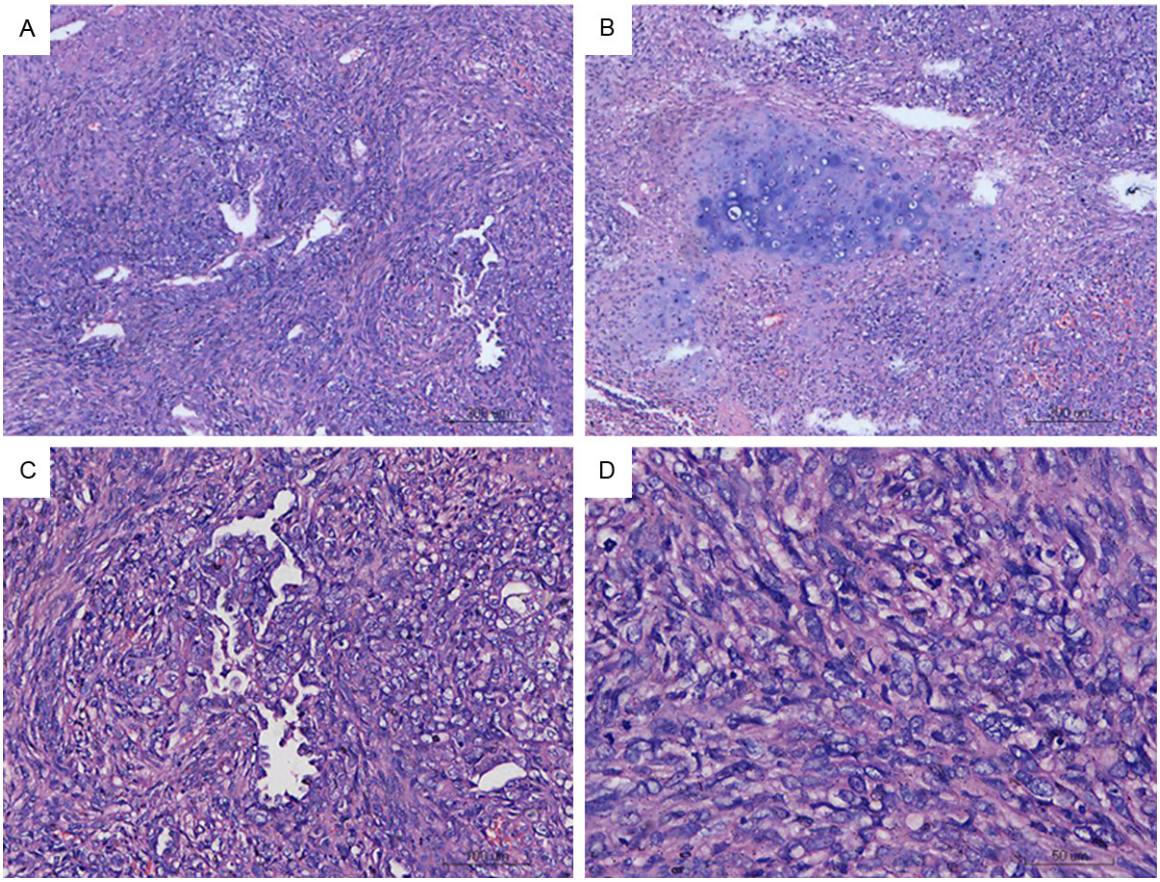

Figure 1. Histopathological features of the biopsy specimen of the uterine tumor. A: The tumor is composed of two components: malignant epithelial and mesenchymal components, HE, ×100. B: Cartilage in mesenchymal component, HE, ×100. C: Endometrioid type adenocarcinoma, HE, ×200. D: Fusiform cell sarcoma, HE, ×400.

of her right breast. Pelvic ultrasound and contrast-enhanced computed tomography revealed that the uterus was bulky in size with an irregular mass in uterine cavity. Additionally, ultrasonography of the right breast demonstrated a hypoechoic nodule, which was suspicious for malignancy in the upper outer quadrant, and revealed enlarged sentinel lymph nodes in the homolateral axilla. There were no abnormal, enlarged, hypoechoic mass or axillary lymph nodes observed by ultrasonography of the left breast, left supraclavicular or infraclavicular areas. For other conditions, fatty liver and calculus on left renal had been observed by ultrasound examination as well. The serum cancer antigen -125 (63.10 U/ml, reference range <35 U/ml) and Alpha fetoprotein (AFP, 22.53 ng/ml, reference range 0-10 ng/ml) level was elevated, while serum carcinoembryonic antigen (0.70 ng/ml, reference range 0.15-9.7 ng/ml) and cancer antigen-199 (8.40 U/ml, reference range <35 U/ml) were normal.

Laparotomy revealed an enlarged uterus, which was adherent to the sigmoid mesocolon. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy and uterine and peritoneal washing for cytological evaluation. Macroscopically, a polypoid mess (6×6×3 cm) arising from the fundus of uterus was observed. Fluid cytology indicated malignant cell found in the uterine washing, and was negative for malignant cells in the peritoneal washing. Histopathological evaluation of the post-surgical specimens of the uterine mass revealed a neoplasm composed of an admixture of malignant epithelial and mesenchymal components (**Figure 1A**, ×100 magnification). The epithelial component was endometrioid type adenocarcinoma (**Figure 1C**, ×200 magnification), while sarcomatous component had heterologous elements including fusiform cell sarcoma (**Figure 1D**, ×400 magnification) and a prominent component of cartilage (**Figure 1B**). There was extensive myometrial invasion

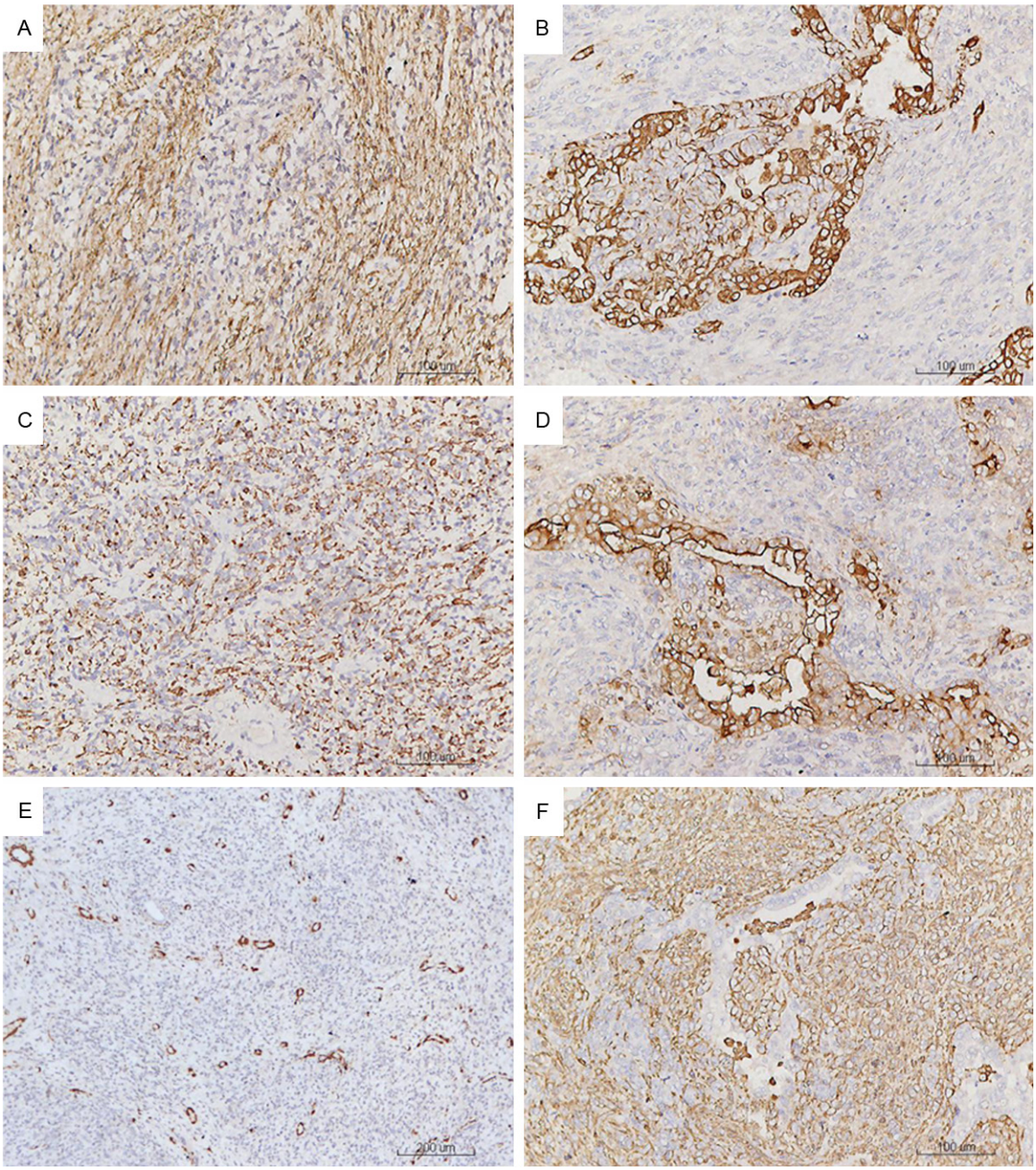

Figure 2. Immunohistochemical features of the uterine tumor. CD10 (A), Desmin (C) and Vimentin (F) were expressed only in the sarcoma component, while positive immunoreactivity for CK (B) and EMA (D) were observed only in the epithelial component, ×200. SMA (E) was negative for sarcoma and epithelial components, ×100.

exceeding the inner half. The oviduct, ovary and bilateral pelvic lymph nodes were negative for malignancy. Therefore, the disease stage IB was identified according to International Federation of Gynecology and Obstetrics (FIGO) classification. To better characterize the different areas of this neoplasm, a panel of immunohistochemical stains outlined different immune marking for the epithelial and mesenchymal component. The epithelial component showed a strong positivity for pancytokeratin (CK, **Figure 2B**) and epithelial membrane antigen (EMA, **Figure 2D**), whereas was negative for CD10 (**Figure 2A**), Vimentin (**Figure 2F**), Desmin (**Figure 2C**) and Scattered smooth muscle actin (SMA, **Figure 2E**). The sarcomatous element

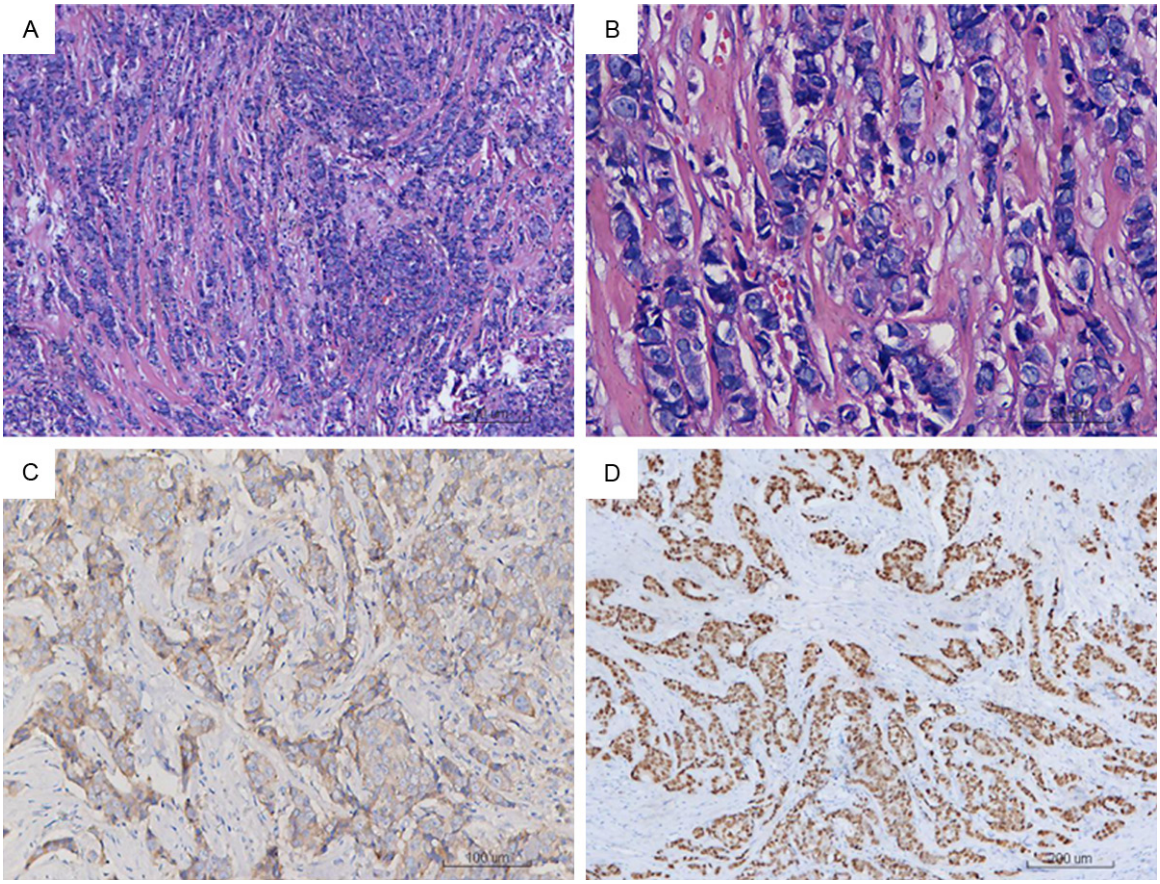

Figure 3. Histopathological and immunohistochemical features of the breast tumor. Characters of tumor cells with HE staining (A, ×100) and (B, ×400). The tumor expressed Her2/Neu (C, ×100) and ER (D, ×100).

was strongly positive for CD10, Vimentin and Desmin, while was negative for CK, EMA and SMA. The pathological report of uterine carcinosarcoma with heterologous elements of endometrial stromal sarcoma and chondrosarcoma had been obtained after integrating histological and immunochemistrical characterises.

She was referred to Department of Surgery in our hospital for evaluation and surgical management 4 weeks later. After extensive discussion, she was underwent modified radical mastectomy of her right breast and axillary lymph node dissection. Pathological report indicated a grade II infiltrating ductal carcinoma on her right breast, with negative margins (**Figure 3A**, **3B**). Five of 12 dissected lymph nodes from the right axilla were positive (Stage III, T3N2M0). The tumor expressed Her2/Neu (**Figure 3C**) and estrogen receptor (ER, **Figure 3D**) but was negative expression for progesterone receptors (PR). The proliferation fraction (Ki-67) was equal to 40%. Due to poor general health conditions, the patient did not undergo administration of adjuvant chemotherapy or radiotherapy. The patient succumbed to the disease approximately 8 months later.

Discussion

The association of breast cancer and uterine carcinosarcoma has been demonstrated by many studies. Total 31 uterine carcinosarcoma cases with exposure to adjuvant tamoxifen after breast cancer have been previously reported in the literature before 2002 [7]. However, concurrence of breast cancer and uterine carcinosarcoma showed extremely rare phenomena, only one case of synchronous endometrial carcinosarcoma and breast carcinoma without the previous use of tamoxifen have been found in literature [8]. To our knowledge, this is the first reported case of this unique combination of synchronous uterine

carcinosarcoma and contralateral breast carcinoma after tamoxifen therapy.

Carcinosarcoma is a rare tumor that shows both epithelial and stromal malignant differentiation. The risk factors for uterine carcinosarcoma include obesity, exogenous estrogen, exposure to radiation and tamoxifen [9]. Carcinosarcoma shares risk factors with breast cancer such as obesity and nulliparity. Recent study indicated nnulliparity and overweight had a synergistic effect on breast cancer risk in elderly women [10], and could enhance risk for second primary contralateral breast cancer [11]. Although tamoxifen is deemed to be the preventive agent of choice in most high-risk premenopausal women, adjuvant tamoxifen therapy for ≥5 years had a 4.4-fold increased risk of ER- contralateral breast cancer [12]. Fatty liver was frequently (30%) found in of patients with breast cancer who received tamoxifen [13], and could appear as early as 3 months after beginning tamoxifen and persist for more than 4 years after discontinuing it [14]. Tamoxifen associated with 14 fold increased risk of carcinosarcoma has been documented [15]. In this present case, the postmenopausal patient had obesity, nulliparity and history of tamoxifen therapy for 5 years. Take them together, risks of contralateral breast cancer and carcinosarcoma should be tallied among the risks of treatment with tamoxifen in elder patients with nulliparity and obesity.

Carcinosarcomas are subdivided into the homologous and heterologous type, based on the histopathologic differentiation of the stromal component of the tumor. Immunohistochemical analyses of various antigens have been performed to evaluate the nature of different malignant components of the uterine carcinosarcoma. Vimentin and Desmin were positive in the sarcomatous portion of carcinosarcoma, focally in the stromal component. CD10 was sensitive immunohistochemical marker of neoplastic endometrial stromal component [16]. Positive staining with CD10 in the fusiform cells which were negative with muscle marker SMA might indicate endometrial stromal sarcoma [17]. Therefore, immunohistochemical staining panel of CD10, Desmin, Vimentin and SMA can be used to support making a definitive diagnosis for carcinosarcoma.

To date, no established guidelines could be referred for the management of uterine carcinosarcomas. The optimal treatment for uterine carcinosarcomas is total abdominal hysterectomy with bilateral salpingo-oophorectomy. In patient with FIGO stage I-II uterine carcinosarcoma, adjuvant chemotherapy is associated with improved progression-free survival have been documented [18]. In patients had stage III to IV, persistent or recurrent disease uterine carcinosarcoma, adjuvant combination chemotherapy with ifosfamide and paclitaxel, paclitaxel and carboplatin should be considered [19-21]. A full understanding of the pathobiogenesis of this tumour is necessary to appraise the aggressive nature of uterine carcinosarcoma and develop molecular-targeted agents for treatment modalities.

Uterine carcinosarcoma are aggressive uterine cancers with poor survival, even when presenting at an apparent early stage with the risk of recurrence being 35-58% in 5 years [22]. The 5-year disease-free survival by stage were 56% for stage I, 31% for stage II, 13% for stage III, 0% for stage IV, with most patients developing extrapelvic disease [21]. Furthermore, the prognosis was poorer in women with contralateral breast cancer than with unilateral breast cancer with the 56% of cumulative breast cancer-specific mortality among women with metachronous bilateral cancer diagnosed within 5 years [23]. Prognosis tends to be worse in this present patient integrated with synchronous uterine carcinosarcoma and contralateral breast carcinoma, which had metastasis of lymph node.

The case report presented here drew the attention of clinicians to the possible of synchronous uterine carcinosarcoma and contralateral breast cancer among women with previous use of tamoxifen therapy. A better understanding of the molecular mechanisms that underlie the development of carcinosarcoma and contralateral breast cancer may lead to improved treatment strategies for survival of those tumors.

Disclosure of conflict of interest

None.

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