Case Report

Carcinosarcoma of the uterus: Possible sequelae of long-term tamoxifen therapy for breast cancer

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ABSTRACT

Carcinosarcoma (CS) of the uterus is rare and accounts for 1–2% of all uterine malignancies, occur commonly in postmenopausal women. These are highly aggressive tumors with poor prognosis and often present at advanced stage. Tamoxifen (TAM) has been known to increase the incidence of endometrial carcinoma from 1 to 2 cases per 1000 women/year and of uterine sarcoma from 0.04 to 0.17 cases per 1000 women/year. TAM has weakly estrogenic properties that can produce endometrial cell proliferation and, consequently, TAM use increases the risk of endometrial cancer by approximately two- to three-fold. Currently, no consensus is present regarding the management of Uterine CS. However, surgery plays an important role in the management along with chemotherapy (CT) and radiotherapy as an adjuvant. We report a case of a woman who developed malignant mixed mullerian tumor of uterus after taking TAM for 6 years as adjuvant hormonal therapy for breast carcinoma.

Key words: Carcinosarcoma, chemotherapy, radiotherapy, tamoxifen, uterus

INTRODUCTION

Carcinosarcoma (CS) of the uterus is rare and accounts for 1–2% of all uterine malignancies, with an incidence of <2/100,000 women per year. Uterine CSs are monoclonal tumors classified as malignant mixed mullerian tumor (MMMT), malignant mesodermal mixed tumors, or metaplastic carcinomas.[1] They occur commonly in postmenopausal women and usually present with abdominal pain, distension, and atypical spotting/bleeding per vaginum. These tumors are highly aggressive and often present with extrauterine spread at Stages III–IV with poor prognosis.

Use of tamoxifen (TAM) has been stated to increases the incidence of endometrial carcinoma from 1 to 2 cases per 1000 women per year, and of uterine sarcoma from 0.04 to 0.17 cases per 1000 women per year.

The management of uterine CS has been controversial. However, as a result of its rarity, surgical management has not been well-defined. Literature review by Vorgias *et al*. in 2010 suggested that the high rates of both local and distant recurrence after surgery essentially need effective adjuvant therapies, although the benefit of adjuvant chemotherapy (CT) or radiotherapy (RT) remains to be determined.

Here, we report a case of woman who developed MMMT of uterus after taking TAM for 6 years as adjuvant hormonal therapy (HT) for breast carcinoma.

CASE REPORT

A 60-year-old postmenopausal para-2 woman presented with complaints of bleeding per vaginum and lower

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abdominal pain for 2 weeks. On physical examination, there was a palpable pelvic mass. Contrast-enhanced computed tomography (CECT), whole abdomen suggested uterine mass with no appreciable lymph nodes [Figure 1a and b].

Ten years before she was diagnosed as a case of high-grade, hormone-receptor positive (estrogen-receptor positive) invasive carcinoma right breast. She underwent modified radical mastectomy and adjuvant CT and RT. After that, she had taken HT with TAM 20 mg once daily for 6 years.

Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) was done. Histopathological examination revealed high-grade CS uterus. Six cycles of adjuvant CT with Paclitaxel and Carboplatin was given. Adjuvant RT was given after six cycles of adjuvant CT. Now the patient is on follow-up for 1 year without any evidence of disease on clinical examination, repeat CECT abdomen and positron emission tomography-scan [Figure 2].

DISCUSSION

Uterine CS is a rare clinical entity, representing <5% of uterine cancer with the median age of presentation is 62 years. There is a very strong association between the TAM treatment and the occurrence of uterine CS. It is evident from the literature that 20 mg/day of TAM over 1 year could be enough to develop uterine sarcoma.[2] Therefore, postmenopausal women taking TAM should be closely monitored for symptoms of endometrial lesions.

CSs are composed of both epithelial and mesenchymal elements. Identification of these two individual components of CSs has led to the concept of their origin.[3] (1) The collision theory, (2) the combination theory, and (3) conversion theory. It is currently believed that CS has a monoclonal origin from a common multidirectional progenitor stem cell, but there remains a percentage of CS with a biclonal origin. An etiological factors implicated in the development of this cancer include prior pelvic exposure to irradiation, obesity, nulliparity, exposure to the human papilloma virus, TAM, and exogenous estrogen.

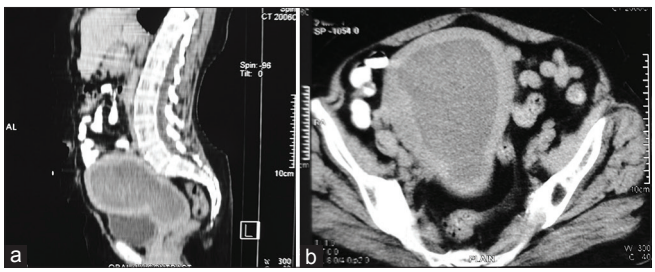

Figure 1: (a and b) Preoperative contrast-enhanced computed tomography pelvis axial and Sagittal view, respectively, showing large uterine mass without any appreciable lymphadenopathy

It is now estimated that 5–30% of patients with CS have a history of pelvic irradiation and is often diagnosed at a latent period of 14 years after irradiation. A typical presentation of CS includes pyometra with vaginal bleeding, watery discharge, abdominal pain, or as a polypoid mass coming out of cervical OS. The "symptom triad" indicative of CS rather than endometrial adenocarcinoma includes pain, severe vaginal bleeding, and the passage of necrotic tissue per vaginum.

Several studies have reported various prognostic factors of uterine CS, including age, stage, lymphovascular space involvement, tumor histology, elevated preoperative CA-125, residual tumor after surgery, positive peritoneal cytology, tumor size, and myometrial invasion.[4] Of patients with localized CS, 20% will be upstaged at laparotomy due to the presence of regional lymph node metastases.[5]

International Federation of Gynecology and Obstetrics staging of MMMTs of the uterus is the same as for endometrial carcinoma. Tumor spread occurs by direct extension to the cervix and vagina followed by other pelvic organs including the bladder and rectum. Lymphatic spread to local and regional lymph nodes appears to occur at an early stage of the disease. Hematogenous spread is also common, usually, to lung, liver, and bone.

Surgery is the cornerstone of treatment, although the extent of the surgical procedure remains unclear. TAH with BSO is the most common procedure; however, the additive benefit of retroperitoneal lymphadenectomy (RLD) remains undetermined.[6] Nemani *et al*. in 2008 reported a significant overall survival (OS) benefit associated with RLD, with a 5-year OS of 49%, compared with 35% for patients who had not undergone RLD.

The high rates of both local and distant relapse after surgery have warranted the need for effective adjuvant treatment.[7] In

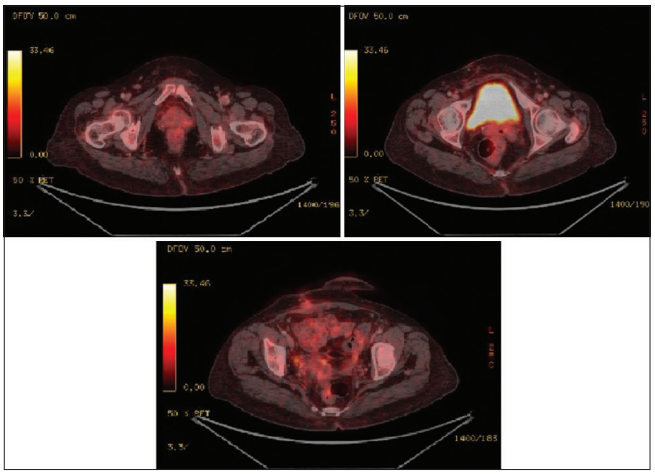

Figure 2: Postoperative positron emission tomography, computed tomography scan showing no residual or recurrence lesion

a series of cases described by Gonzalez Bosquet *et al*.,[8] surgery followed by sequential treatment yielded a significantly longer median DFS versus surgery, RT or CT alone. Menczer *et al*.[9] published a multi-center retrospective study comparing CT with or without radiation to RT alone in patients, who underwent surgical staging. The authors reported that sequential treatment after surgery decreased mortality, as compared to patients taking RT or CT alone. The 5-year OS rate for all stages of uterine CS varies from 10% to 69%.

Historically, ifosfamide has been the most effective CT agent. Recently, phase III trial by Gynecologic Oncology Group (GOG) in 2007 reported that the use of cisplatin plus ifosfamide CT compared favorably over whole abdomino-pelvic radiation as adjuvant therapy in all stages of CS. The results of a recent phase II GOG trial in 2010 suggested that a combination of paclitaxel and carboplatin is also a tolerable and effective regimen.[10]

CONCLUSION

Uterine CS warrants complete surgical staging and clinical assessment followed by systemic therapy in both early and advanced diseases excluding patients with noninvasive disease. CT is effective in the advanced and metastatic stage of disease. Enough evidence is present to support the use of pelvic radiation and/or vaginal brachytherapy with or without CT for surgical I and II stage patients.

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Conflicts of interest
There are no conflicts of interest.

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