Uterine Carcinosarcoma in A BRCA2 Mutation Carrier

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Abstract

Background: Uterine carcinosarcoma is one of the most aggressive uterine cancers, with 5-year survival for advanced stage disease of 30%. Currently, there is no optimal standard chemotherapy regimen for uterine carcinosarcoma and most patients suffer from disease recurrence.

Case Presentation: A 68 year-old Ashkenazi Jewish woman was diagnosed with stage IIIC2 uterine carcinosarcoma after presenting with abdominal pain. Although uterine carcinosarcoma is not currently associated with any genetic syndrome, her ancestry and family history of breast cancer prompted genetic screening. She was found to be a carrier of the BRCA2 mutation. After surgical resection and chemotherapy with carboplatin/paclitaxel, she had complete response and has had disease free survival for over 23 months.

Conclusion: We report prolonged disease free survival of uterine carcinosarcoma in BRCA2 mutation carrier.

Introduction

Uterine carcinosarcomas, also known as malignant mixed Mullerian tumors, are comprised of both epithelial and mesenchymal components [1]. Carcinosarcomas are aggressive tumors representing 5% of uterine malignancies and are responsible for 16% of uterine cancer deaths [1]. Radiation therapy and tamoxifen use are known factors associated with development of uterine carcinosarcoma [2,3]. Uterine carcinosarcoma has not been associated with a genetic syndrome.

A review of PubMed publications with keywords uterine carcinosarcoma, BRCA2, BRCA1 and tamoxifen revealed two reports of patients with uterine carcinosarcoma and BRCA2 mutation. One patient with a BRCA2 mutation had a diagnosis of uterine carcinosarcoma with a history of tamoxifen use [4]. Another study identified two patients with BRCA1 related breast cancer who subsequently developed uterine carcinosarcoma in the absence of tamoxifen use [5]. Here we describe the first patient with BRCA2 mutation and diagnosis of uterine carcinosarcoma without history of exposure to tamoxifen.

Case Presentation

A 68 year old Ashkenazi Jewish woman presented with complaints of abdominal pain, anorexia, and alternating diarrhea and constipation. She also reported significant fatigue and a six-pound unintentional weight loss. Evaluation led to a diagnosis of irritable bowel syndrome and the patient was treated with minimal relief. The patient then presented with symptoms of progressive constipation. She underwent further evaluation with a CT of the abdomen and pelvis revealing a large uterine mass compressing the sigmoid colon. Pelvic ultrasound showed a 16 cm uterus with cystic areas. She was referred to a gynecologic oncologist, whose examination revealed a 16-week size uterus with nodularity and no adnexal masses.

The patient underwent an exploratory laparotomy and intraoperative findings included a large mass appearing to originate from the ovary adherent to the cul-de-sac, sidewalls and sigmoid colon mesentery. Frozen section favored sarcoma, therefore, she had a total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node sampling and peritoneal biopsies. Cytology of the peritoneal washings was negative for malignancy and final pathology revealed carcinosarcoma arising from the uterine fundus (Figure 1 and 2a) with metastases to both ovaries (Figure 3) and left fallopian tube (Figure 4). Pathologic examination revealed the mass originating from the uterine fundus containing both sarcomatous and carcinomatous...
The left ovary, left fallopian tube and bilateral pelvic lymph nodes and left para-aortic lymph nodes were positive for metastatic adenocarcinoma yielding a final diagnosis of Stage IIIIC2 grade 3 carcinosarcoma of the uterus. Following optimal surgical resection of the tumor, the patient underwent combination chemotherapy with carboplatin and paclitaxel for 3 cycles then pelvic radiation therapy followed by an additional 3 cycles of carboplatin and paclitaxel therapy.

Evaluation of the patient’s family history revealed a maternal aunt with breast cancer diagnosed in her fifth decade. No other family history of cancer was reported. Due to her Ashkenazi Jewish ancestry, family history of breast cancer and personal uterine cancer diagnosis, though atypical for the BRCA1/2 mutation, she elected to have a sample sent for genetic testing. She was found to be a carrier of the BRCA2 5946delT (6174delT) mutation, one of three founder mutations in the Ashkenazi Jewish population.

Discussion

Uterine carcinosarcoma has been associated with BRCA2 mutations in patients with prior exposure to tamoxifen [4]. The case presented here provides evidence of the first uterine carcinosarcoma associated with germline BRCA2 mutation in the absence of tamoxifen exposure. Although this case of uterine carcinosarcoma may be sporadic, the patient’s prolonged disease free survival after being treated with platinum based agents may be a result of her germline BRCA mutation-related hypersensitivity to platinum chemotherapy agents.

Studies by the Gynecologic Oncology Group found efficacy of adjuvant chemotherapy in uterine carcinosarcomas with regimens of ifosfamide and cisplatin; paclitaxel and carboplatin; and ifosfamide and paclitaxel [6,7]. However, the optimal chemotherapy...
regimen has not yet been demonstrated. Our patient, who received adjuvant chemotherapy with paclitaxel/carboplatin and interval radiation therapy, has progression free survival of 23 months since chemotherapy. Her survival exceeds the median reported survival of 16 months of a phase II trial of carboplatin and paclitaxel in women who received adjuvant therapy for unmeasurable disease [8]. Of note, long-term survival after complete response to cisplatinum and ifosfamide has been reported in a patient with BRCA2 tamoxifen associated uterine carcinosarcoma [4].

It is important to note that assigning the site of origin for a tumor involving multiple contiguous organs is difficult. This usually relies on assessment of relative tumor volumes and in some cases histopathologic evidence of premalignant lesions demonstrating transition to malignancy. In the case presented, the pattern of distribution was consistent with uterine origin with bilateral ovarian and left fallopian tube metastases. The possibility of synchronous ovarian tumors or Mullerian field effect could not be completely excluded and it is noted that ovarian carcinosarcoma has been associated with BRCA2 mutation in one case report [9]. However, it is important to note that although the right ovary was replaced by sarcomatous tumor, the right fallopian tube and right para-aortic lymph nodes did not contain malignancy, a finding that does not support a right ovarian primary malignancy in this patient.

This case report is the first to suggest an association of BRCA2 mutation with uterine carcinosarcoma in absence of tamoxifen exposure. Further studies are needed to determine the prevalence of BRCA mutations in uterine carcinosarcomas and whether loss of heterozygosity is present in these tumors. If further studies support an association between uterine carcinosarcoma and BRCA2 mutations, concomitant hysterectomy at the time of risk-reducing bilateral salpingo-oophorectomy in women with known BRCA2 mutations may be considered.

References