Clinics in Oncology

Case Report
Published: 14 Oct, 2016

Uterine Carcinosarcoma in A *BRCA2* Mutation Carrier

Petersen SS[1], Quigg MH[2], Zhang Z[3] and Buekers T[4]*

[1]*Department of Women's Health Services, Henry Ford Hospital, USA*

[2]*Department of Medical Genetics, Henry Ford Hospital, USA*

[3]*Department of Pathology, Henry Ford Hospital, USA*

[4]*Division of Gynecology Oncology, Department of Women's Health Services, Henry Ford Hospital, USA*

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 *BRCA* 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

OPEN ACCESS

Correspondence:
Thomas E. Buekers, Division of Gynecologic Oncology, Department of Women's Health Services, Henry Ford Hospital, 2799 West Grand Boulevard, K9 Detroit, Michigan, 48202, USA, Tel: 313- 916-2465; Fax: 313-916-1239; E-mail: tbueker1@hfhs.org

Received Date: *28 Aug 2016*
Accepted Date: *11 Oct 2016*
Published Date: *14 Oct 2016*

Citation:
Petersen SS, Quigg MH, Zhang Z, Buekers T. Uterine Carcinosarcoma in A BRCA2 Mutation Carrier. Clin Oncol. 2016; 1: 1111.

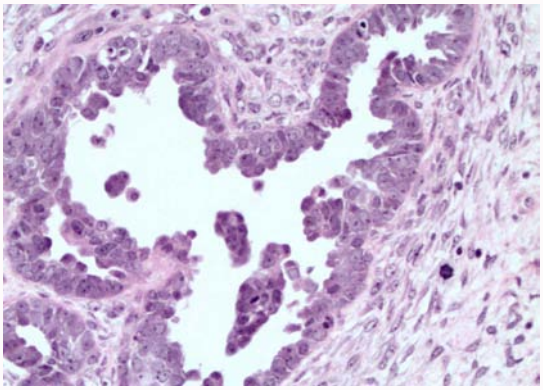

Figure 1: Carcinoma element of uterine tumor: Malignant glands form papillary fronds and exhibit high grade serous morphology with markedly nuclear pleomorphism and prominent nucleoli.

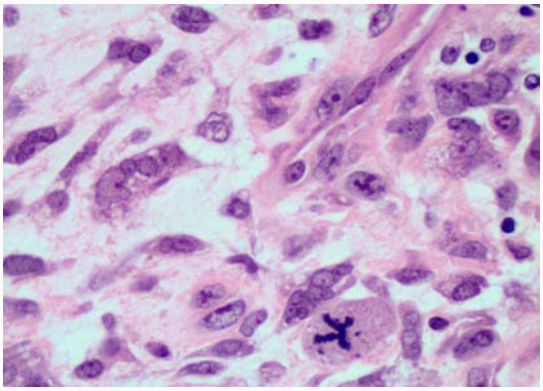

Figure 2a: Sarcomatous element of uterine tumor: Malignant cells form sheets with little cytoplasmic differentiation. They show bizarre high grade nuclei with brisk mitotic activities; some demonstrate rhabdoid morphology with eosinophilic cytoplasm.

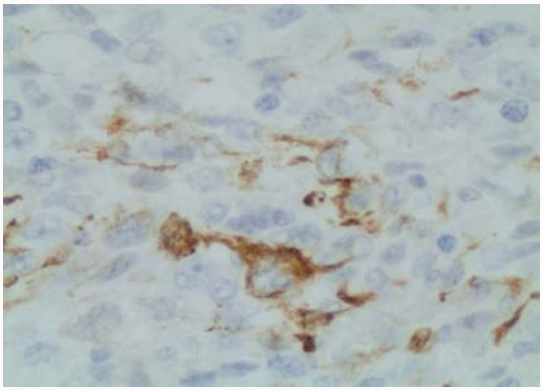

Figure 2b: Sarcomatous element of uterine tumor: stain positive for Desmin.

histologic components, confirmed with immunohistochemical staining of desmin (Figure 2b), vimentin, CD10 and AE1/AE3. The right ovary was completely replaced with tumor predominately composed of myxoid sarcomatous components and right fallopian tube was negative for malignancy.

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 IIIC2 grade 3 carcinosarcoma of the uterus. Following optimal surgical resection of the tumor, the patient underwent combination chemotherapy with

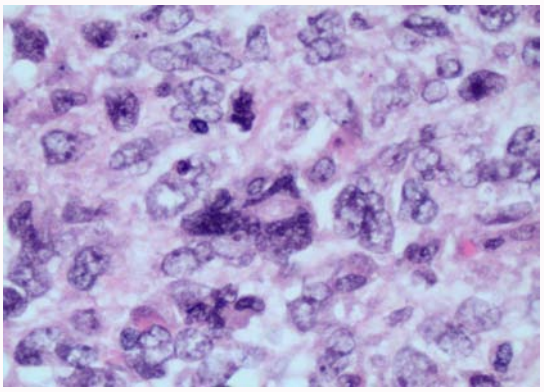

Figure 3: Tumor metastasis to ovaries: Mainly composed of sarcomatous element, identical in morphology to sarcomatous portion of uterine tumor.

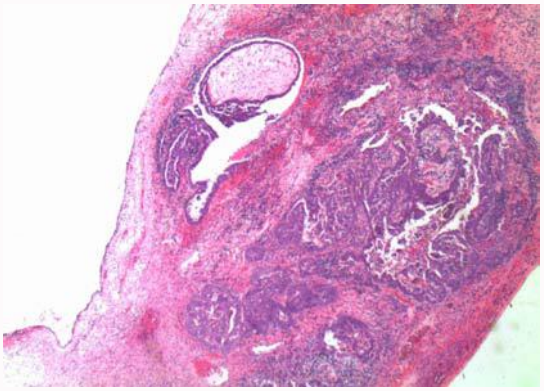

Figure 4: Tumor metastasis to fallopian tube wall: Composed of malignant glands with high grade serous morphology, identical to carcinoma element of uterine tumor.

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 *BRCA*1/2 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

1. Artioli G, Wabersich J, Ludwig K, Gardiman MP, Borgato L, Garbin F. Rare uterine cancer: carcinosarcomas. Review from histology to treatment. Critical reviews in oncology/hematology. 2015; 94: 98-104.
2. Meredith RF, Eisert DR, Kaka Z, Hodgson SE, Johnston GA Jr, Boutselis JG. An excess of uterine sarcomas after pelvic irradiation. Cancer. 1986; 58: 2003-2007.
3. Olah KS. Uterine carcinosarcoma in association with tamoxifen therapy. British journal of obstetrics and gynaecology. 1997; 104: 1420.
4. Clara A, Fonseca I, Francisca A, Bettencourt A, Vaz F. Unexpected long-term survival in a BRCA2 patient with metastatic carcinosarcoma associated with tamoxifen. Gynecologic oncology case reports. 2013; 4: 44-46.
5. Wilson BT, Cordell HJ. Uterine carcinosarcoma/malignant mixed Mullerian tumor incidence is increased in women with breast cancer, but independent of hormone therapy. Journal of gynecologic oncology. 2015; 26: 249-251.
6. Wolfson AH, Brady MF, Rocereto T, Mannel RS, Lee YC, Futoran RJ, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol. 2007; 107: 177-185.
7. Powell MA, Filiaci VL, Rose PG, Mannel RS, Hanjani P, Degeest K, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin oncol. 2010; 28: 2727-2731.
8. Lacour RA, Euscher E, Atkinson EN, Sun CC, Ramirez PT, Coleman RL, et al. A phase II trial of paclitaxel and carboplatin in women with advanced or recurrent uterine carcinosarcoma. Int J gynecol cancer. 2011; 21: 517-522.
9. Sonoda Y, Saigo PE, Federici MG, Boyd J. Carcinosarcoma of the ovary in a patient with a germline BRCA2 mutation: evidence for monoclonal origin. Gynecol Oncol. 2000; 76: 226-229.