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Case Report
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Uterine Carcinosarcoma after Pelvic Radiotherapy

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Abstract

Radiation is a treatment of many gynecologic malignancies, especially locally-advanced cervical cancer. Development of second malignancies is a rare complication of radiotherapy. Our patient had uterine carsinosarcoma20 years after radiotherapy for cervical cancer. Two theories of radiation-induced malignancies were described: direct damage of double strand DNA and the abscopal or indirect damage. No difference in treatment of second cancer (uterine carsinosarcoma) from primary cancer is recommended. However, poor pelvic blood supply form previous radiation may affect tissue healing and the delivery of adjuvant chemotherapy. Our patient had poor prognosis with advanced stage at the time of presentation, rapidly progressed after completion of treatment, and died only 11 months after diagnosis.

Uterine carcinosarcoma or malignant mixed mullerian tumor is a biphasic tumor composed of high-grade carcinoma and sarcoma elements [1]. It is a rare gynecological neoplasm (< 5% of all uterine malignancies) [1]. The median ages of diagnosis reported among published series ranged from 62-67 years [2]. The prognosis of uterine carcinosarcoma is poor with a 5-year overall survival of only 30% [3]. Several risk factors for carcinosarcoma were tamoxifen therapy, long-term unopposed estrogen usage, previous radiotherapy, and etc. History of previous pelvic radiotherapy was discovered as high as 37% of carcinosarcoma patients [3].

We reported a patient with advanced-stage uterine carcinosarcoma after a long interval after pelvic radiation for cervical cancer. The clinical, radiographic, pathologic features, management and outcome of the patient were presented.

Case Presentation

A 61-year-old woman, P2, sought for medical care in our institution for her post-menopausal bleeding symptom in July 2015. She had a history of cervical cancer, FIGO stage IIB, and completed radiotherapy 20 years ago. No other past or current medical illnesses were reported. Physical examination revealed uterine enlargement without any evidences of pelvic, intra-abdominal or systemic abnormalities. Endometrial biopsy demonstrated high grade carcinoma, not otherwise specified.

Additional investigations showed elevated CA-125 to 146.5 U/ml. The magnetic resonance imaging (MRI) showeda large endometrial mass, sized 7.5 x 9.1 x 9.3 cm, with high signal intensity on T2Wwith invasion to inner half of myometrium and extended to endocervix. There were no evidences of tumor extension to uterine serosa, parametrium, adnexae, bladder, rectum, or lymphadenopathy. She had complete surgical staging with total abdominal hysterectomy, bilateral salpigo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy and peritoneal washing for cytology. The operative findings showed necrotic mass, sized 6 x 5 x 3 cm occupying the entire uterine cavity invading to outer half of myometrium with extension to lower uterine segment and who lecervix. Aside from a 2-cm tumor noduleat omentum, no other gross lesions were noted. The surgery was optimal without any gross residual diseases. Estimated blood loss was 700 ml. Surgical mesh was placed in the pouch of Douglas to prevent vaginal cuff dehiscence.

Pathological report showedendometrioid carcinoma admixed with high grade malignant mesenchymal structures. Both malignant epithelial and sarcoma components were demonstrated infiltrating fallopian tubes, ovaries, omentum as well as all pelvic and para-aortic lymph nodes. Numerous foci of lymphovascular space invasion (LVSI) were reported.Peritoneal washing was also positive for carcinoma cells. Immunohistochemical stainingof the tumor showed positiveepithelial membrane antigen (EMA), cytokeratin (CK),vimentin,andestrogen receptor (ER) while negative progesterone receptor (PR). The final diagnosis was carcinosarcoma of the uterus, FIGO stage IVB.

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Postoperative course was uneventful. Paclitaxel 175 mg/m^2 and carboplatin AUC 6 were given for 6 cycles before pelvic radiation as adjuvant therapy. There were no evidences of diseases by physical examination and transvaginal pelvic ultrasonography after completion of treatment. CA-125 was 33.5 U/ml. Three months later, she developed abdominal discomfort. Physical examination showed marked ascites and a 4-cm supravaginal stump pelvic mass. Her CA-125 elevated to 173.4 U/ml. Computerize tomography (CT) showed pelvic mass, sized 3.8 x 4 cm locating in mid lower pelvis with bladder wall thickening, and circumferential rectal and long segmental bowel wall thickening. Large amount of ascites and carcinomatosis peritoneiwere also noted. Taken into consideration her cancer prognosis and poor performance status (ECOG 3), only palliative progestin with intermittent abdominal paracentesis to relieve symptoms were given. She consequently developed obstructive nephropathy, uremia and died11 months after surgery.

Discussion

Radiation is a mainstay of treatment for locally-advanced cervical cancer, as the sole treatment in the past and concurrent with chemotherapy at present. Many complications from radiation are recognized especially long-term complications which increase over time [4]. One important consequence of radiation, albeit uncommon, is second malignancy of pelvic organs e.g. cancers of the bladder, rectum, vagina, cecum, bone, and the uterine corpus [5]. A review of 1,089 patients with various sarcomas at the UCLA Medical Center showed 37 patients had received prior radiotherapy [6]. Among these, 12 originated from the uterus including: six carcinosarcoma, fourleiomyosarcoma, and each one of endometrial stromal sarcoma, and angiosarcoma [6]. Mean interval from radiotherapy to the development of carcinosarcomaranged from 3 years to 30 years [1,6].

The mechanism of radiation-induced malignancies was not fully understood. Two mechanisms were proposed for the pathogenesis of radiation-induced malignancies. With low-dose radiation exposure, radiation single and double strand DNA breaks occur. The double strand DNA breaks lead to gene mutation and malignant transformation of the radiated cell [7]. On the other hand, the occurrence of cancer after high-dose radiation exposure is explained the bystander or abscopal effect.The release of soluble factors and charged particles from radiated cells cross the gap junction into the normal cells. This induced inflammatory cytokines resulting in a release of reactive oxygen causing DNA damage [8].

There have been no standard criteria for a diagnosis of radiotherapy-associated cancer. Some proposed the following issues for diagnosis (i) the development of sarcoma must be within a previously irradiated field; (ii) patients should have received a significant amount of radiation; (iii) a latency period of several years (at least 3-5 years) must elapse between the time of radiation and the development of the sarcoma; (iv) the diagnosis of the sarcoma must behistologically proven; and (v) the second sarcoma should have different histopathology from the primary neoplasm [9,10].

The second cancer of our patient met all of these proposed criteria of radiotherapy-associated cancer. She had completed course of radiation including external beam pelvic radiation and brachytherapy. These 2 radiation means should deliver the total dose of 85-90 Gyto pelvis [11]. Her uterine sarcoma developed20 years after radiation. Lastly, the histopathologies of the first and second cancers were clearly different, squamous cell carcinoma vscarcinosarcomarespectively. We would like to add that there were no other well recognized predisposing factors for uterine carcinosarcoma, such as, obesity, diabetes mellitus, or metabolic syndrome, etc. which may contribute to the cause of carcinosarcoma [2,12].

Probably from a limited number of this event and reports, there have been no specific descriptions of clinical presentation and morphology of the radiotherapy-associated cancer. Abnormal uterine bleeding may be primarily hidden by cervical stenosis after radiation, so the patientsfrequently present with enlarged uterus and advanced stage at diagnosis.Poor wound healing is generally recognized as a common postoperative problem in previous radiation area [4]. We were aware of this possibility, so preventive measure with surgical mesh was done and there was no postoperative complications.

The prognosis of the patient with carcinosarcoma is worse than high-grade endometrial carcinoma [2]. Several prognostic factors were reported: stage of disease, type and grade of carcinoma, tumor size, depth of myometrial invasion, lymphovascular invasion, adnexal spread, cervical involvement, lymph node metastasis, and type of treatment especially adjuvant treatment [2,13,14]. Adjuvant treatment is generally indicated in all stages of uterine carcinosarcoma even in stage I because of high recurrence rate.However, there is no consensus with regard to the optimal mode of adjuvant treatment (chemotherapy or radiation or both) [12]. Our case had completed courses of both radiation and chemotherapy (6 cycles of carboplatin and paclitaxel) after surgery [15-18]. Although there were no clinical evidences of cancer after treatment, her diseases rapidly reappeared soon within a month. This was probably due to the tumor aggressive behavior and her advanced stage at diagnosis. Poor pelvic blood supply form previous radiationmay hinder the delivery of adjuvant treatment to affected areas, could not eradicate all microscopic residual tumors, and further worsen her prognosis. Her diseases recurred very soon after cessation of treatment.

Hormonal treatment may have some role in uterine carcinosarcoma especially in those with positivehormone receptor [19]. One study trial by Wang et al. reported good response rate of recurrent uterine carcinosarcoma to letrozole therapy [20]. The primary tumor in our patient had positive estrogen receptor despite negative progesterone, but her recurrence cancer showed no-response to high-dose progestin with progressive diseases and death 2 month after recurrence.

Conclusion

Uterine carcinosarcoma after previous radation therapy is a rare condition. Management is the same as endometrial carcinoma but the prognosis is worse. Advanced stage at presentation and unhealthy pelvic tissue may be the factors in surgical complication, unresponsive treatment and very poor prognosis.

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