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Case Report

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Cervical Malign Mixed Mullerian Tumor Treated by Post-operative Radiotherapy and Chemotherapy: A Case Report

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ABSTRACT

Cervical cancer remains a leading cause of cancer-related mortality, particularly in developing countries. Malignant mixed Mullerian tumor (MMMT) of the cervix is an exceedingly rare biphasic malignancy, comprising both epithelial and stromal components. We report a case of cervical MMMT. A 47-year-old postmenopausal woman presented in May 2015 with spontaneous vaginal bleeding. Contrast-enhanced magnetic resonance imaging of the lower abdomen revealed a 44x17 mm contrast- enhancing mass at the level of the uterine cervix. Following the biopsy, the patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and omentectomy in March 2016. Histopathology confirmed a cervical MMMT. The patient received adjuvant radiotherapy to the pelvis, followed by chemotherapy. At the nine-year follow-up, the patient remains disease-free with no long-term radiation-induced toxicity. Surgery remains the primary treatment for cervical MMMT, while adjuvant radiotherapy and chemotherapy may provide clinical benefits in selected cases.

Keywords: Cervical cancer, malign mixed mullerian tumor, postoperative radiotherapy

Introduction

Cervical cancer is a major cause of oncology-related deaths worldwide, especially in developing regions. While the incidence of human papillomavirus-associated cervical cancer has declined in developed nations due to robust screening and vaccination programs [1,2]. Squamous cell carcinoma (SCC) accounts for 80-90% of malignant neoplasms detected in the cervix; adenocarcinoma and less common adenosquamous carcinoma, sarcoma, melanoma, lymphoma and small cell carcinoma account for the remaining 10-20% [3-5]. Malignant mixed Mullerian tumor (MMMT) of the cervix is a very rare entity, first described by Ferriera [6] in 1951. MMMT is a biphasic tumor and contains both epithelial and stromal components [7,8]. The most common location of the disease in the female genital tract is the uterine corpus [9,10]. We report a case of cervical MMMT that was successfully managed with surgery followed by postoperative radiotherapy and chemotherapy.

Case Report

A 47-year-old postmenopausal woman with a history of rheumatoid arthritis presented in May 2015 with several months of spontaneous vaginal bleeding. Informed consent was obtained from all participants. Physical examination revealed a palpable cervical mass. Contrast-enhanced magnetic resonance imaging (MRI) of the lower abdomen revealed a 44x17 mm contrast-enhancing mass at the level of the uterine cervix, with suspected parametrial invasion (Figures 1 and 2). A contrast-enhanced computed tomography (CT) scan of the lower abdomen revealed a 47x38 mm mass in the cervix, with obliteration of the fatty planes between the mass and the posterior rectum (Figure 3). A cervical biopsy was performed, and a malignant mesenchymal tumor of the cervix was diagnosed. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and omentectomy were performed in March 2016. On microscopic examination, a biphasic tumor was observed, consisting of

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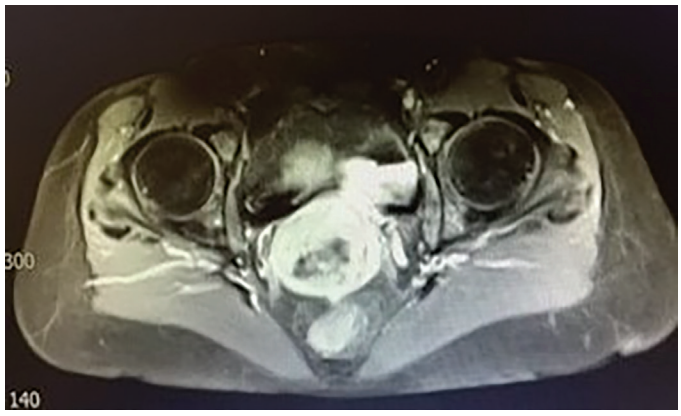

Figure 1. Axial T1 contrast-enhanced pelvic MR section showing cervical mass with suspicion of parametrial invasion
MR: Magnetic resonance

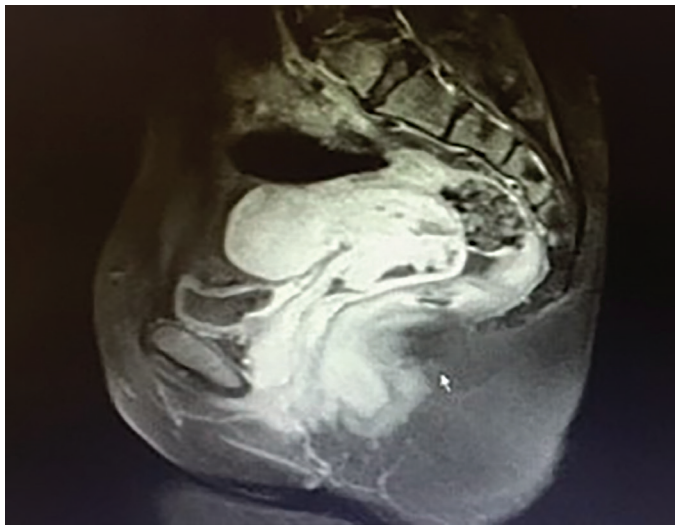

Figure 2. Sagittal T1 contrast-enhanced pelvic MR section showing cervical mass
MR: Magnetic resonance

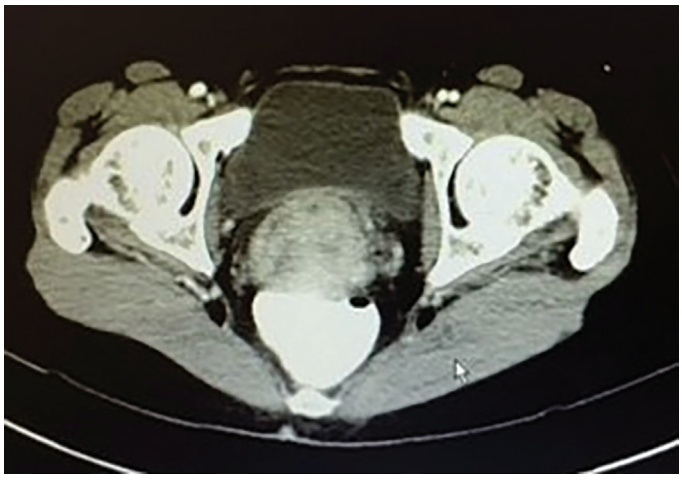

Figure 3. Contrast-enhanced lower abdomen CT scan abdomen revealed a mass in the cervix with obliteration of the fatty planes between the mass and the rectum posteriorly
CT: Computed tomography

epithelial islands composed of atypical cells with abundant cytoplasm and an intervening proliferation of atypical spindle cells. High mitotic activity was noted in both components. On immunohistochemical staining, the epithelial areas were cytokeratin-positive, whereas the spindle cells were vimentin-positive. Based on these findings, the case was diagnosed as a MMMT (Figure 4). Postoperative positron emission tomography-CT showed no evidence of distant metastasis. The disease was found to be in the International Federation of Gynecology and Obstetrics 1B2 (pT1b2N0) stage. Between 07/06/16 and 13/07/16, 45 Gy/25-fraction external radiotherapy was applied to the pelvic lymphatics, the upper third of the vagina, the vaginal cuff, and the parametrium using the volumetric arc therapy technique with 6 megavolt energy (Figure 5). The common iliac, internal iliac, external iliac, and obturator lymph nodes were included in the treatment area. Grade 1 genitourinary and gastrointestinal side effects were observed during radiotherapy. Toxicity grading was performed according to the Radiation Therapy Oncology Group toxicity scale [11]. After radiotherapy, the patient received carboplatin (area under the curve 5), paclitaxel (175 mg/m^2) for four cycles every 21 days between 07/09/16-14/11/16. The patient developed a grade 2 hematologic side effect due to chemotherapy; the treatment was adjusted. The patient was followed up in accordance with cervical cancer follow-up protocols. She was examined at the outpatient clinic every 3 months for the first 2 years, every 6 months for 3-5 years, and annually thereafter. Contrast-enhanced pelvic MRI or CT scans were performed every 6 months for the first 2 years and annually thereafter. Annual vaginal and cervical cytology was performed. The patient's follow-ups are ongoing. No signs of recurrence were detected on the contrast-enhanced CT scan performed in the 9th year of follow-up (Figure 6). The patient continues to live free of disease and radiotherapy-related long-term toxicity.

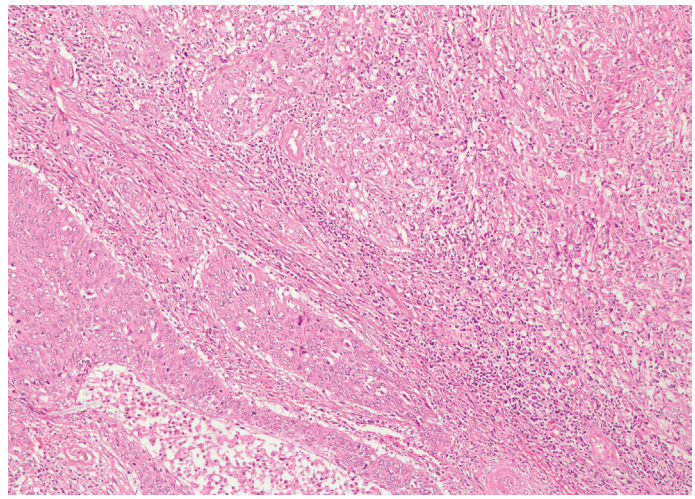

Figure 4. Histopathological examination of the mass. Epithelial and mesenchymal components together; left: epithelial, right: mesenchymal

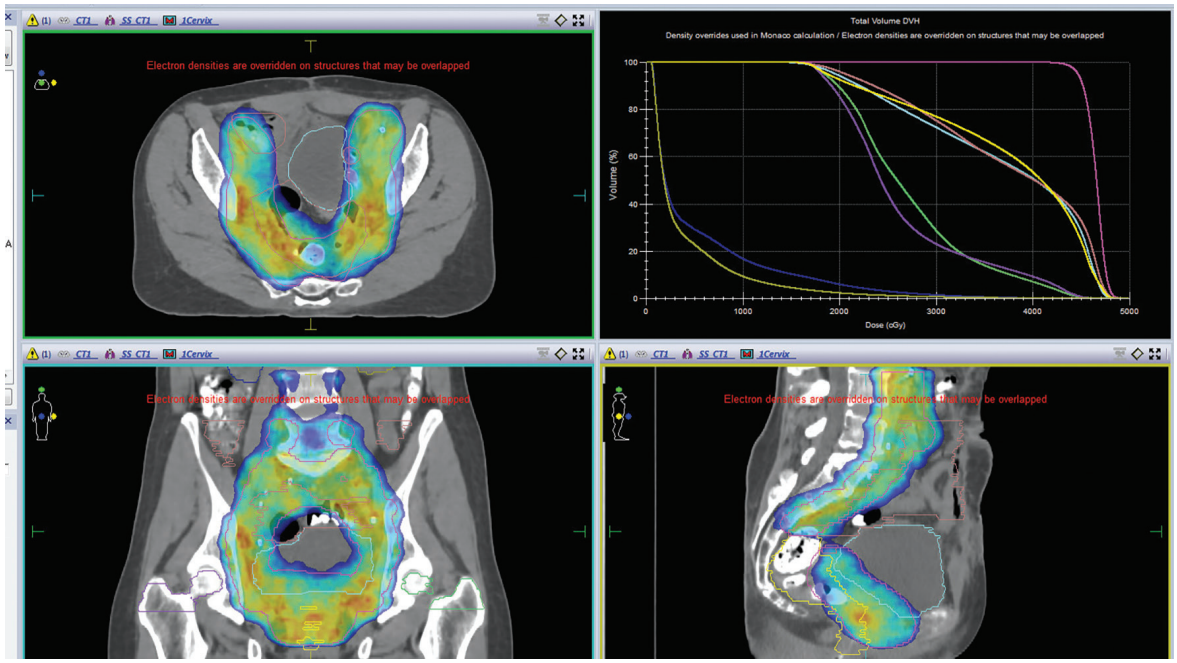

Figure 5. Radiotherapy planning image and dose-volume histogram

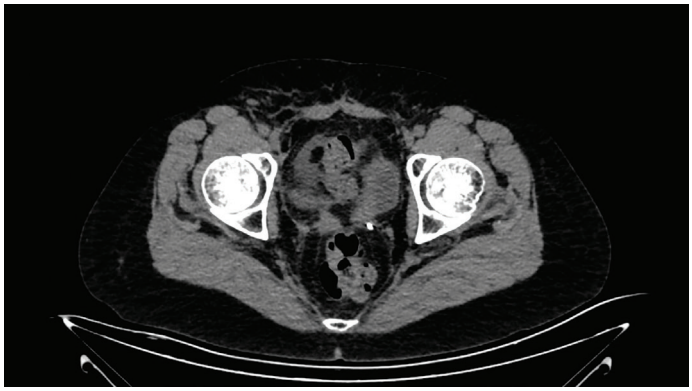

Figure 6. No signs of recurrence were detected on the contrast-enhanced CT scan performed in the 9th year of follow-up
CT: Computed tomography

Discussion

MMMT of the cervix is extremely rare. In the female genital tract, MMMT most commonly arises in the uterus but can also arise in the cervix, vagina, ovaries, and fallopian tubes. Outside the genital tract, it can be detected as de novo peritoneal involvement. MMMT of the cervix usually occurs during the postmenopausal period. Although the average age of onset is 61-69 years, reported ranges in the literature span 12-93 years. It frequently presents with abnormal vaginal bleeding [10,12]. MMMT is a biphasic tumor containing epithelial and mesenchymal components. The epithelial component may consist of SCC, adenocarcinoma, adeno-squamous carcinoma, adenoid cystic carcinoma, undifferentiated carcinoma, or a mixture of these. The mesenchymal component may be homologous or heterologous. The epithelial component determines the prognosis of the disease [9,10,12,13]. Cervical MMMT is more often confined to the cervix and uterus at presentation.

In the study by Kudela et al. [5], a 65-year-old patient diagnosed with cervical MMMT underwent radical hysterectomy and pelvic lymphadenectomy followed by 60 Gy/30 fraction whole pelvis irradiation and adjuvant cisplatin-based chemotherapy. The patient continues her life, disease-free, in the fifth year after the operation. Sharma et al. [7], evaluated five patients who received treatment for cervical MMMT. One patient was in stage 4B and died of disease progression shortly thereafter. Of the remaining patients, two were diagnosed at stage 1B1 and the other two were diagnosed at stage 1B2. Two patients with stage 1B1 underwent radical hysterectomy: one with pelvic lymphadenectomy, and the other with bilateral salpingo-oophorectomy and pelvic lymphadenectomy followed by adjuvant radiotherapy. One of the patients with stage 1B2 underwent radical hysterectomy and pelvic lymphadenectomy, while the other received only 45 Gy/25 fraction pelvic radiotherapy and brachytherapy. The follow-up periods of these patients were 65, 35, 42, and 28 months, respectively. All four patients continue to lead their lives disease-free. Clement et al. [10], evaluated nine patients diagnosed with cervical MMMT. The stage of eight of these patients could be determined: seven were staged as 1B and one was staged as 2B. Among six patients, five underwent hysterectomy with lymphadenectomy. One of these patients received postoperative radiotherapy, and another received postoperative radiotherapy and chemotherapy. The remaining three patients underwent local excision; lymphadenectomy was performed in one. One of these patients received postoperative radiotherapy, and another received postoperative radiotherapy and chemotherapy. Follow-up was possible in seven patients, and recurrence was observed in two. Patients with recurrence were those who underwent a hysterectomy and lymph node dissection as primary treatment. In one of these patients, a vaginal recurrence was observed in the third year, and excision

and radiotherapy were performed as treatment for the recurrence. The patient continues to live with her tumor after 4.5 years of follow-up. The other patient experienced pelvic recurrence at nineteen months. This patient died at 3.5 years of follow-up due to disease progression. One patient died of colon cancer in year 13. Four patients remain disease-free.

Due to its rarity, there is no evidence-based treatment guideline for cervical MMMT. Radical surgery is recommended for the primary treatment of the disease. Some authors recommend pelvic lymph node dissection [5]. In our case, pelvic lymph node dissection and omentectomy were performed. Although adjuvant radiotherapy and chemotherapy have produced favorable results, the role of these modalities remains unclear. In our case, radiotherapy and chemotherapy were administered after surgery. In early-stage disease, cure is possible with treatment, but the prognosis is poor in extracervical disease.

Because of its rarity, cervical MMMT may pose a challenge to clinicians during diagnosis and treatment. It is important to adopt a multidisciplinary approach to the care of these patients. According to the available literature, primary surgery and, if necessary, adjuvant radiotherapy and/or chemotherapy seem to be the appropriate treatment.

Conclusion

Surgery remains the primary treatment for cervical MMMT, while adjuvant radiotherapy and chemotherapy may provide clinical benefits in selected cases. As the number of cases reported in the literature increases, a consensus on treatment can be reached.

Ethics

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.U.A., İ.A.Ç., Ş.F.E., Concept: S.U.A., Design: S.U.A., İ.A.Ç., Data Collection or Processing: S.U.A., İ.A.Ç., Analysis or Interpretation: S.U.A., İ.A.Ç., Ş.F.E., Literature Search: S.U.A., İ.A.Ç., Writing: S.U.A., İ.A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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