ABSTRACT

Aims: Endometrial cancer usually occurs after perimenopause and is associated with obesity, diabetes, hypertension, nulliparity, and anovulatory menstrual cycles. Abnormal vaginal bleeding is an early symptom of endometrial carcinoma. We describe our experience with a patient who had endometrial cancer that developed 27 years after radiation therapy for cervical carcinoma, without vaginal bleeding.

Presentation of Case: The patient was a 45-year-old woman with stage IIIB uterine cervical cancer who received radiation therapy. She presented with lower abdominal pain 27 years after treatment.
Both transvaginal ultrasonography and magnetic resonance imaging showed a tumor within the uterus. Endometrial biopsy revealed endometrial adenocarcinoma. After placement of a double-J stent, abdominal total hysterectomy and bilateral salpingo-oophorectomy were performed.

**Discussion and Conclusion:** Our experience shows that endometrial carcinoma can develop 27 years after radiation therapy for cervical cancer. Moreover, patients who have endometrial cancer after radiation therapy might have no abnormal bleeding despite the presence of gross tumor because radiotherapy leads to stenosis and occlusion of the vagina and cervical canal. We should be aware that endometrial adenocarcinoma has an atypical course after radiation therapy; long-term observation is thus essential.

**Keywords:** Endometrial cancer; radiation therapy; uterine cervical cancer.

**1. INTRODUCTION**

Endometrial cancer occurring after radiation therapy for cervical carcinoma is extremely rare. It is well known that abnormal vaginal bleeding is present as an early symptom of endometrial carcinoma in nearly all patients. We report a case of endometrial carcinoma that developed 27 years after radiation therapy for Stage IIIB cervical carcinoma. Our patient had no abnormal vaginal bleeding despite the presence of gross tumor.

**2. CASE**

A 45-year-old woman presented with Stage IIIB squamous cell carcinoma of the cervix. The tumor extended to the left pelvic wall. She received external beam radiotherapy (EBRT) to the whole pelvis and high-dose-rate intracavity brachytherapy (HDR-ICBT). EBRT was started alone without the use of midline shield until 40 Gy was delivered; HDR-ICBT was performed later. EBRT to a total dose of 50 Gy was delivered in 2 Gy per fraction, treating daily, 5 fractions a week. HDR-ICBT was performed with one or two insertions per week, for a total of 5 fractions, along with the midline shield. A dose of 6 Gy in one fraction was routinely prescribed to point A. Follow-up examinations were performed at regular intervals for 7 years, without relapse. She had never received hormone-replacement therapy. The patient had abdominal discomfort 27 years after radiotherapy and visited her neighborhood hospital. Transvaginal ultrasonography revealed hydrometra, and magnetic resonance imaging (MRI) showed a large amount of fluid and a high-intensity mass in the uterus (Fig. 1). She was referred to the Division of Gynecology of our hospital. Gynecologic examination showed that the uterine corpus had enlarged to more than fist-size. There was no free space in the bilateral parametrium, and decreased mobility of the uterus was confirmed on rectal examination. The proximal vagina was closed, and the cervix could not be identified. MRI was conducted, and a 150 ml volume of wine-colored fluid within the uterine cavity was drained by making an incision in the swollen vaginal wall; a tumor was found to deeply invade the myometrium (Figs. 2A, B). After placement of a double-J stent, abdominal total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was filled with tumor. Histopathological examination revealed moderately differentiated (G2) endometrioid adenocarcinoma, with clear-cell changes on hematoxylin and eosin staining (Fig. 3). Tumor invaded the cervical stroma and near the serosa of the corpus uteri.

**Fig. 1. MRI before drainage. Sagittal T2-weighted MRI, showing a large amount of fluid and a high-intensity mass in the uterus (arrow)**
Second, patients in whom endometrial cancer develops after radiation therapy for cervical cancer might have no abnormal bleeding despite the presence of gross tumor in the uterine cavity.

First, endometrial carcinoma can occur 27 years after radiation therapy for cervical cancer. Several reviews estimate that the incidence of endometrial carcinoma developing after pelvic irradiation ranges from 0.1% to 1.1% [1,2]. The mean latency period between radiotherapy and the diagnosis of endometrial cancer was 15 years, and the maximum period was 30 years [2,3]. To our knowledge, a latency period of 27 years between radiation therapy and the development of endometrial cancer is the second longest interval to be reported.

The uterus usually receives a total dose of 45 to 50 Gy during radiation therapy for cervical cancer, which generally causes complete and irreversible ablation of the endometrium [4]. Some residual functional endometrium, which gave rise to endometrial cancer, might have remained even after curative radiation therapy in our patient. Patients who received unopposed estradiol as hormone replacement therapy after radiation in whom regular vaginal blood loss developed and histological examination showed proliferative endometrium have been previously documented by de Hullu et al. [5]. Moreover, another study reported that active endometrial tissue was found in 62.5% of patients who had uterine bleeding after radiation therapy [6].

There are two potential explanations for resistance of the endometrium to the effects of radiation [7]. First, the distance from the endometrium to the brachytherapy source is very variable. Any distortion of the cavity caused by tumor, myoma, or other factors as well as by differences in the size of the uterus would also lead to variations. Namely, the farther the distance from the radiation source, the weaker would be the effect of radiation. The second hypothesis is that the stage of the menstrual cycle during which treatment is initiated may have an effect. It is more likely that G0 cells will survive radiation than cells in late S phase or mitosis.

The second important point shown in the present case is that patients in whom endometrial cancer develops after radiation therapy for cervical cancer might have no abnormal bleeding despite the presence of gross tumor in the uterine cavity.
Abnormal uterine bleeding is known to occur in approximately 90 percent of women with endometrial carcinoma [8]. This clinical finding, which is associated with even intraepithelial lesions in contrast to cervical cancer, enables the early detection of most cases of endometrial carcinoma. However, Pothuri et al. [3] reported that endometrial cancer was diagnosed at an early stage (International Federation of Gynecology and Obstetrics stages I and II) in only 6 of 24 patients who had received radiation therapy. Radiotherapy often causes marked fibrosis and shrinkage of the uterus, as well as stenosis or occlusion of the vagina and the cervical canal [4,9]. Radiation-induced cervical stenosis may prevent the drainage of any blood in the uterus, leading to symptoms such as abdominal pain and cramping. Our patient also presented with abdominal pain due to hematometra, not vaginal bleeding, which helped us find the gross tumor in the uterine cavity.

Kumar et al. [10] pointed out that radiation-associated endometrial cancers are more likely to be non-endometrioid adenocarcinoma and carcinosarcoma rather than second sporadic endometrial cancers. In other words, they suggested that these high-grade histologic types have intrinsic aggressive tumor biologic behavior. They also showed that a similar tendency is associated with endometrial cancer developing after irradiation of tumors located in adjacent body sites (such as the colon and rectum, urinary system, vulva, anus, and vagina). Although the histopathological diagnosis was endometrial carcinoma, and the latency period to diagnosis was 27 years in our patient, physicians should be aware that endometrial adenocarcinoma arising after radiation therapy has an atypical presentation and histological features.

4. CONCLUSION

We described our experience with a case of endometrial cancer that developed 27 years after radiation therapy for cervical carcinoma in a woman who had no abnormal bleeding despite the presence of gross tumor. Patients who have received radiation therapy for not only cervical cancer but also for other malignancies should undergo long-term follow-up, even in the absence of vaginal bleeding, bearing in mind the risk of endometrial carcinoma.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ota T, Takeshima N, Tabata T, Hasumi K, Takizawa K. Treatment of squamous cell carcinoma of the uterine cervix with radiation therapy alone: Long-term survival, late complications, and incidence
of second cancers. Br J Cancer. 2007;97:1058-62.

2. Gallion HH, Van Nagell JR Jr, Donaldson ES, Powell DE. Endometrial cancer following radiation therapy for cervical cancer. Gynecol Oncol. 1987;27:76-83.

3. Pothuri B, Ramondetta L, Martino M, Alektiar K, Eifel PJ, Deavers MT, et al. Development of endometrial cancer after radiation treatment for cervical carcinoma. Obstet Gynecol. 2003;101:941-5.

4. Piksi S, Martin KO. Hormone replacement after gynecological cancer. Maturitas. 2010;65:190-97.

5. de Hullu JA, Pras E, Hollema H, van der Zee AG, Bogchelman DH, Mourits MJ. Presentations of endometrial activity after curative radiotherapy for cervical cancer. Maturitas. 2005;51:172-6.

6. Barnhill D, Heller P, Dames J, Hoskins W, Gallup D, Park R. Persistence of endometrial activity after radiation therapy for cervical carcinoma. Obstet Gynecol. 1985;66:805-8.

7. Habeshaw T, Pinion SB. The incidence of persistent functioning endometrial tissue following successful radiotherapy for cervical carcinoma. Int J Gynecol Cancer. 1992;2:332-335.

8. Seebacher V, Schmid M, Polteraue S, Heffler-Frischmuth K, Leipold H, Concin N, Reinthaller A, Heffler L. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: A retrospective multi-center study. BMC Cancer. 2009;9:460.

9. Vernooij CB, Kruitwagen RF, Rodrigus P, Kock HC, Feyen HW. Hematometra after radiotherapy for cervical carcinoma. Gynecol Oncol. 1997;67:325-327.

10. Kumar S, Shah JP, Bryant CS, Seward S, Ali-Fehmi R, Morris RT, et al. Radiation-associated endometrial cancer. Obstet Gynecol. 2009;113:319-25.