Second Primary Genital Squamous Cell Carcinoma Following Cervical Cancer Treatment

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Abstract

Recently with more effective treatment strategies for cervical cancer, larger numbers of patients survive and greater incidence of second malignant neoplasms have been diagnosed. Patients after treatment of cervical cancer have a 2.5-37% lifetime risk of developing a second squamous cell malignancy of the lower genital tract (1). This risk is 5 to 12 times higher compared to general population (2). In our case report we attempted to analyze clinical characteristics of a patient with vulvar carcinoma following cervical cancer treatment with particular focus on the etiology such as HPV, radiation therapy and genetic instability, prognostic factors and treatment result.

Keywords: cervical cancer, second primary genital cancer, radiotherapy, HPV

Özet

Serviks Kanseri Tedavisinden Sonra İkinci Primer Skuamöz Hücreli Genital Kanser

Son zamanlarda serviks kanseri için etkili tedavi stratejileri uygulanması ile daha çok sayıda hastanın sağ kalması sağlanmış ve ikinci malign neoplazma insidansı artmıştır. Serviks kanseri tedavisi olmuş hastalarda hayat boyu alt genital sistemde ikinci skuamöz hücreli kanser gelişme riski %2.5-37'dir (1). Bu risk genel popülasyona kıyasla 5 ilâ 12 kat kadar daha yüksektir (2). Olgu sunumumuzda serviks kanserini takiben vulva kanseri gelişen olguda HPV, radyoterapi ve genetik kararsızlık gibi etyolojik faktörlere odaklanarak, prognostik faktörleri ve tedavi sonucunu analiz etmeyi amaçladık.

Anahtar sözcükler: serviks kanseri, ikinci primer genital kanser, radyoterapi, HPV

Introduction

Increased numbers of long term survivors of gynecologic malignancy resulted in increased attention in second malignant neoplasms. Patients after treatment for gynecologic malignancy have a 3-6% lifetime risk of developing a second unrelated malignancy such as lung, bladder, connective tissue, kidney, esophagus, small intestine, rectum, bone and other genital organs (3). Prevalence of second genital primary cancer varies between 2.5 and 37%. In the study of Storm second primary cancer was assessed among 24 970 women with invasive cervical cancer and 19 470 women carcinoma *in situ* of the cervix by using data from the population-based Danish Cancer Registry (2). In this study, the risk of developing second lower genital tract cancer in cervical carcinoma patients was 5 to 12 times higher, compared to the general population. Therapy for the primary tumor, genetic instability or common environmental factors such as smoking and HPV may attribute as causative agents in second malignant neoplasms.

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Case Report

A 58-year-old female admitted to our hospital with a complaint of vaginal bleeding in 1997. An uceroevegetan tumor was observed in the cervix and colposcopy assisted biopsy was performed subsequently. Non keratinizing squamous cell carcinoma was diagnosed in pathologic study. Vagina and cervix were analyzed for HPV DNA types by DNA in situ hybridization. The examination revealed a HPV type 16 positivity. In gynecologic examination, it was decided that the tumor involved both parametriums and reached to the side walls of pelvis and that was confirmed by abdominal MRI. Therefore, A stage IIIB cervical cancer was classified according to FIGO Clinic Staging System. An external pelvic radiotherapy and brachytherapy were performed to our case (total 60 Gy). In 2003, the patient presented with an hypertrophic and contact bleeding, 2-3 cm in diameter vulvar lesion that involvies the clitoris (Figure 1). A punch biopsy was performed and in the histo-pathologic study, the lesion was defined as papillary squamous cell carcinoma. Abdominal MRI, cystoscopy and rectosigmoidoscopy were performed and no pathology was found. Class I vaginal smear was defined. The disease location didn't include urethra, vagina and anal canal and there was no suspected palpable lymph node in pelvic examination. Therefore, a stage II vulvar can-

cer was classified according to FIGO Clinic Staging System and a surgical treatment was decided. Radical vulvectomy and bilateral inguinal lymphoadenectomy were performed (Figure 2). Pathologically, a papillary squamous cell carcinoma with low-grade differentiation was reported. According to FIGO Surgery Staging System, in the surgery it was classified as stage II tumor due to no tumoral invasion to surgical borders, vessels and lymphnodes. The performed surgical treatment was accepted as curative. One year following the treatment the patient was reevaluated by abdominopelvic MRI, and punch biopsy was taken from the previous excision site. There was no evidence of additional tumor progression or dissemination. She is currently disease-free.

Discussion

Some investigators reported that the ionizing radiation may induce second cancer in radiation fields (4). The overall relative risk in patients treated with radiation therapy was 1.1 for developing cancer in organs that received high radiation exposures (bladder RR:3.5; rectum RR:1.8, genital sites other than ovary and uterine corpus RR:3.2) (5). A significant increase in vulvo-vaginal cancer was also noted in Kapp's analysis of 763 patients with invasive carcinoma of the cervix treated predominantly with radiation therapy (6). Radiation induced cancer is defined as second cancer developed in the irradiated field with a latency period of at least 2 years after radiation therapy. Tatsuo Arai and his colleagues suggested that the minimum latent period of second cancer is somewhere between 2 to 5 years (4). Whereas Czesnin and his colleagues report that excesses in risk appear after a latency interval of 10 or more years (7). Therefore longer follow-up should be mandated for cervical cancers treated with radiation therapy since these patients are at risk to develop second radiation related cancer.

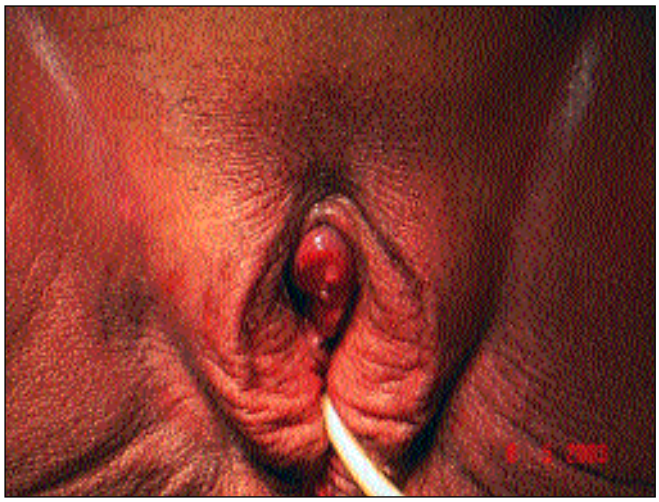

Figure 1. Primary vulvar squamous cell carcinoma following radiation therapy for cervical cancer.

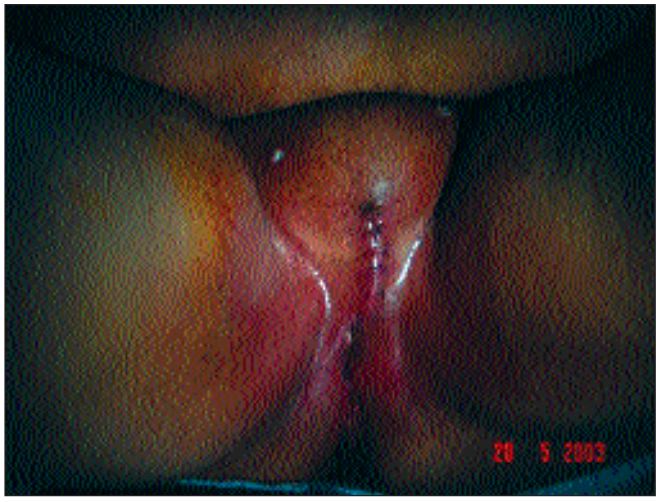

Figure 2. Demonstration of the patient after radical vulvectomy and bilateral inguinale lymphadenectomy were performed.

The common risk factors including genetic susceptibility for the cervix appears to be associated with squamous cell carcinomas of lower genital tract as well. The lower anogenital tract, which includes the uterine cervix, vagina, vulva and anus consists of contiguous surface of epithelium that is derived embryologically from urogenital sinus and cloacal ectoderm (8). HLA region definitely establishes the presence of susceptibility locus in this region for patients with squamous cell carcinomas and emphasizes the association of DQB1, DQA1 and DRB1 (9). Genetic mutations that determine susceptibility to lower genital tract cancers have been studied. After identification of p53 protein, overexpression of p53 was found to cause oncogenic transformation of cells. Overexpression of p53 gene was detected in both cervical and vulvar carcinoma. P53 mutation appears to be one of the most important oncogenic event for vulvar carcinomas (10). HPV and cigarette smoking are suspected to be responsible for the increased risk for the second lower genital cancers (11). The anatomic continuity of the lower genital tract appears to be associated with a shared potential for exposure to putative carcinogenic agents. Different strains of HPV have been reported in different hystologic types of cervical, vaginal or vulvar cancer, with chronic infection with HPV 18 being more commonly associated with adenocarcinomas and HPV 16 with squamous cell carcinoma (8). Cycle regulator genes could be co-operating with human papilloma virus genes in the induction and progression of gynaecological cancers. Also immunosupression as a result of an underlying disease process or exposure to systemic chemotherapy or smoking may also increase susceptibility to viral induced cancers in the lower genital tract.

Carcinogenesis sensitivity of lower genital tract increases because of common genetic mutations and genetic susceptibility, depressed immune system, radiotherapy or combination of these three factors. As a fourth inductive agent HPV, can be strongly anticipative about second primary genital tumors in the future. However, we need more discriminative studies about each factor's effect on carcinogenesis. We suggest analyzing of all cervical carcinoma patients for HPV DNA and longer follow-up should be mandated for patients treated with radiation therapy.

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