Research Article

ISSN 2689-1093

Surgical Research

Osteonecrosis of the Hip, a Complication of Radiation Therapy in Cervical Cancer: Case Study and Literature Review

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Received: 14 Nov 2024; **Accepted:** 17 Dec 2024; **Published:** 24 Dec 2024

Citation: Alshakankery Safaa, Ellathy Hala, Alghamdi Susan, et al. Osteonecrosis of the Hip, a Complication of Radiation Therapy in Cervical Cancer: Case Study and Literature Review. Surg Res. 2024; 6(6): 1-4.

ABSTRACT

Introduction: *Cervical cancer is reported as the fourth most common cancer among females worldwide after breast, colorectal, and lung cancer. In Saudi Arabia it is the eighth most common form of cancer among females aged 15 to 44 years. Squamous cell carcinoma is the most common subtype of cervical cancer, followed by adenocarcinoma. Radiotherapy has a principal role in the management of locally advanced cervical cancer, either as an adjuvant treatment after surgery in the presence of risk factors or as a primary curative treatment, used in combination with chemotherapy and a brachytherapy boost to the primary site.*

Radiotherapy for patients with cervical cancer has been used as an effective cure and increasing rates of long-term survival. Pelvic Radiation can cause variable side effects on pelvic organs including the small bowel, rectum, anus, bone and bone marrow, bladder, urethra, ureter, vulva, vagina, uterus, ovaries, and sexual organs.

Aim: *The aim of this report is to present a case of femoral head necrosis after a therapeutic pelvic irradiation of cervical cancer to draw physicians' attention to that clinical problem which continues to be underestimated. It is necessary to consider bone structures among organ at risk (OAR) involved in irradiation fields and differentiate the bone changes secondary to radiation exposure from bone metastasis, also differentiate radiation-induced sarcoma as late complication to avoid improper management.*

Case Report: *A 35-year-old female was diagnosed with locally advanced squamous cell carcinoma of the cervix (international Federation of Gynecology and Obstetrics International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1) after she presented to the gynecologist complaining of post-coital vaginal bleeding and intermenstrual bleeding.*

The patient received chemoradiotherapy followed by brachytherapy. After completion of treatment, she had a follow up radiological imaging which revealed a complete radiological and pathological response. During her routine follow-up, she complained of tingling electric pain with numbness referred to her back and lower limbs, PET scan revealed non avid right femoral head and right ala of the sacrum lesions likely post radiotherapy osteonecrosis. Follow up after 3-months with MRI pelvis confirmed the diagnosis of post radiotherapy osteonecrosis.

Conclusion: *The radiotherapy tends to be used to treat advanced stage cervical cancer, and these patients usually do well clinically. However, radiation exposure can initiate regional complications to the exposed pelvic organs. Pelvic bone osteonecrosis is a serious complication of pelvic radiation which may affect patients' quality of life and requires more attention.*

Keywords
Osteonecrosis of the hip, Radiation therapy complications, Cervical cancer, Femoral head necrosis, Avascular necrosis.

Introduction
Globally, cervical cancer is the fourth most common cancer in women, after breast, colorectal, and lung cancer, and the eighth-most common form of cancer among female aged 15 to 44 years in Saudia Arabia, with observation of increased number of cases over the last 5 years, and about 358 new cervical cancer cases are diagnosed annually in Saudi Arabia (estimations for 2020) [1,2]. Cervical cancer ranks as the 9th leading cause of cancer deaths of female cancer deaths in Saudi Arabia [2].

The WHO Global strategy to reduce the number of new cases annually to 4 or fewer per 100 000 women and sets three targets to be achieved by the year 2030: through vaccination, screening, and proper treatment of women with cervical disease [1]. Management of local/locoregional disease depends on the local stage of the disease, Surgical therapy is only considered in patients with earlier stages of cervical cancer (up to FIGO IIA) without risk factors necessitating adjuvant therapy [3]. Chemoradiotherapy (CRT) in locally advanced cervical cancer has been the standard of care for patients with bulky IB2–IVA disease [3]. Adjuvant treatment in patients with intermediate-and high-risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy [3].

Brachytherapy is an integral entity of definitive treatment for patients with locally advanced cervical cancer with reported higher survival rate and improved outcome [4].

There is no precise safe dose or tolerance dose in radiotherapy, however there are various factors that increased the risk of radiotherapy inducing bone complications such as; previously irradiated atrophic bone, second malignancy, infection, radiation dose, age, menopausal status, underlying bone weakness, corticosteroid use, smoking, low body mass index, previous fracture, hormonal replacement therapy and chemotherapy [5].

Radiation-induced pelvic bone complications are frequent and well understanding of characteristic imaging patterns is essential; to avoid misinterpretation and inaccurate management. Spectrum of pelvic bone complications post radiation therapy includes focal red marrow changes, pelvic insufficiency fracture, radiation osteitis, and avascular necrosis. Radiation-induced sarcoma is a rare late complication which should be taken in mind [6].

Bone is a dynamic tissue with a strict integral role between osteoblasts and osteoclast cells which are responsible for bone homeostasis. Radiation has a direct effect on bone cells including the destruction of osteoblasts, osteocytes, and osteoclasts which decrease the collagen production and alkaline phosphatase activity resulting in decreased bone mineralization and leaves an acellular matrix which explains the pathogenesis of the radiation upon osseous structures [7]. Radiation also affects the microvasculature of the mature bone; causing decreased blood supply which results in ischemic bone changes. These two processes can lead to significant clinical and radiographical bone atrophy, resulting injuries include non-traumatic pelvic bones fracture, osteitis, and osteonecrosis [7]. The mechanisms of radiation may produce carcinogenic changes that are caused by gene mutations, or changes in gene expression without mutations [8]. An adequate management, early diagnosis and prompt, proper treatment may protect patients from long-term radiation morbidities.

Case Study
A 35-year-old female, medically free, presented to the gynecologist complaining of intermenstrual bleeding and post coital bleeding for 1 year. Pap-smear was done revealed squamous cell carcinoma. Pelvic examination under general anesthesia revealed hard indurated bloody cervix with expansion of the cervical canal with 4 cm mass, and upper two thirds of vagina was involved with left parametrial involvement.

Cervical biopsy demonstrated invasive moderately differentiated squamous cell carcinoma. Pelvic magnetic resonance imaging (MRI) revealed a 4 cm mass directly infiltrating the upper third of vagina with parametrial invasion and metastatic left external iliac lymph nodes compatible with international Federation of Gynecology and Obstetrics (FIGO) staging (IIIC1). Computed tomography (CT) scan of chest, abdomen and pelvis for staging showed no distant metastasis, apart from enlarged left external iliac lymph nodes.

Positron Emission Computed tomography (PET CT) showed marked FDG avid cervical mass with avid left external iliac lymph node and no PET evidence of distant metastasis. The case was discussed in the multidisciplinary tumor board meeting and the decision was definitive concurrent chemoradiation 56 Gy, simultaneous integrated boost (SIB) to involve pelvic nodes with high dose rate (HDR) Brachytherapy boost to central disease to 85 Gy cumulative dose. Six months later after completion of treatment MRI and PETCT were done which showed complete radiological response. During her next follow up visits to the clinic the patient was complaining of tingling electric pain and numbness referred to the back of her lower limbs down to the ankle more at the right side. PETCT was repeated which revealed lucent lesions with sclerotic margin at the right femoral head and right ala of the sacrum likely representing post pelvis radiotherapy osteonecrosis which was confirmed with MRI without evidence of metastasis. Follow up with (MRI) pelvis after 3 months demonstrates stable bone lesions in keeping with post pelvis radiotherapy osteonecrosis grade 2. The patient was referred to the orthopedic team for supportive treatment.

Discussion
Radiation therapy is now widely used as the treatment of choice for the locally advanced carcinoma cervix [9]. Advanced radiation protocols help in delivery of very accurate dose distribution and precise beam delivery However, early, and late effects of irradiation still constitute significant issue in clinical practice [7]. Late effects

after pelvic radiation can occur from 3 months to many years after treatment [10]. Radiotherapy induced bone complication are including bone marrow changes, Insufficiency fracture, Osteitis, osteonecrosis, and radiation induced sarcoma [11]. Osteonecrosis is considered as one of the most challenging long-term complications in radiotherapy, also called aseptic necrosis, ischemic necrosis, or avascular necrosis (AVN) [7]. The incidence of pelvic post radiotherapy necrosis varies widely, ranging from 2.1 to 34%, depending on the radiotherapy technology and standards applied [12]. The latency period for the development of radiation-associated sarcoma is typically 5–20 years, it accounts for 0.5–5% of all sarcomas. the most common radiologic findings included a soft-tissue mass (96%), bone destruction (83%), tumor matrix mineralization (48%), and periosteal reaction (31%). For bone lesions, radiation osteitis is the main differential diagnosis, but radiation osteitis does not have an associated soft-tissue mass in most cases [13]. Early detection of avascular necrosis of the femoral head allows conservative treatment to be effective, with relief of pain and preservation of normal joint function [14]. Nuclear bone scan is not specific for osteonecrosis as radiotracer activity can be seen in both metastasis and osteoarthritis while MRI is the modality of choice for evaluation of radiation induced bone complications due to high diagnostic accuracy, as reported in previous studies, MRI has high sensitivity and specificity reaching up to 95% and 77 % respectively [15]. The principal role of MRI imaging is in establishing the diagnosis of AVN in symptomatic patients before radiographic changes become apparent. MRI imaging can also depict early stages of AVN in high-risk, asymptomatic patients or in the asymptomatic contralateral hips of patients with known AVN [14]. The MRI findings of avascular necrosis usually appear as geographic subchondral lesion with or without double line sign, predominantly at the anterosuperior aspect of the femoral head.

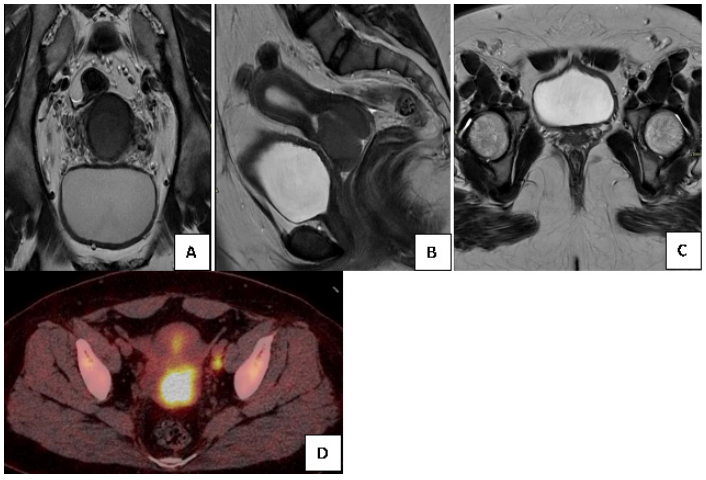

Figure 1: Pre-management MRI pelvis (A) coronal T2, (B) sagittal T2 and (C) axial T2 images at the time of presentation before treatment, demonstrates an endophytic cervical mass (white arrows), normal signal pattern is noted within the femoral heads at both sides. (D) PETCT image revels intensely avid cervical mass (blue arrow) and avid left external iliac lymph node.

The management of bone femoral head AVN depends on the stage and extend of the findings, so meticulous radiological assessment and accurate reporting are mandatory to deliver the proper management. Radiologically the hip osteonecrosis can be classified by different classifications the widely used is Steinberg classification [16]. The goals in treatment of femoral head necrosis are to relieve pain and preserve the femoral head as long as possible [17]. Non-operative treatment for early stage involves restricted weight bearing using a cane and activity modification. These methods only work in the early stage, but show limited success in preventing disease progression [17]. Other conservative treatments, including the use of pharmacological agents (such as lipid lowering drugs, anticoagulants, vasodilators, traditional Chinese medicines, and bisphosphonates) [14]. Operative treatments include Core decompression and bone grafting, are the leading surgical treatment for pre-collapse osteonecrosis of femoral head. Osteotomies are used to rotate the necrotic or collapsing segment of the hip out and replace them with a healthy viable bone. Arthroplasty, Limited femoral resurfacing with cement fixation is usually used in younger patients [14].

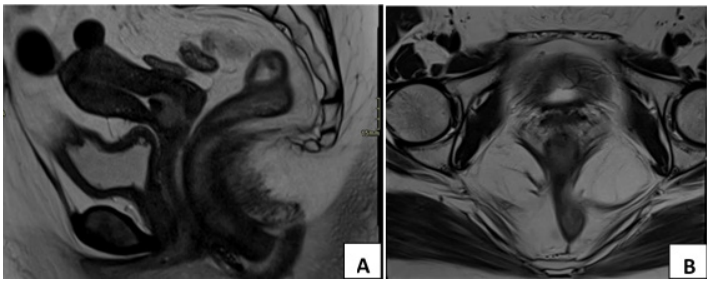

Figure 2: Post management MRI pelvis (A) sagittal T2 image demonstrates significant interval regression of the cervical mass, (B) coronal T2 image reveals normal signal pattern within the femoral heads.

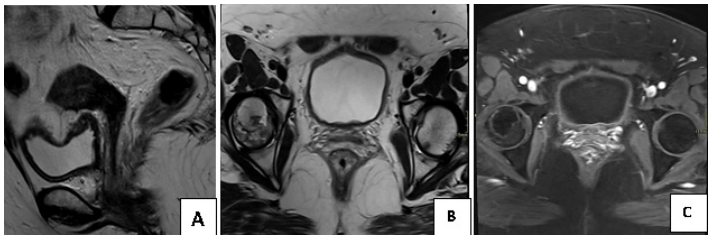

Figure 3: 6 months later follow up MRI pelvis (A) sagittal T2 image revels complete resolution of the cervical mass. (B) axial T2 image revels right femoral head a second hyperintense inner line between normal marrow and ischemic marrow; this appearance is highly specific for osteonecrosis of the hip and is known as the "double-line sign" (C) axial T1 image with contrast revels areas of low signal intensity in the right femoral head representing oedema, bordered by a hyperintense line that represents blood products characteristic for osteonecrosis grade 2.

Conclusion

Osteonecrosis seems to be infrequent side-effect of radiotherapy; however, it may lead to sever functional impairment in those patients. An early diagnosis and proper treatment may protect patients from long- term morbidities. Pre-radiation bone marrow densitometry (BMD) and assessment of other risk factors are an

important pre-management work up to assess the risk of radiation toxicity on the bone structures at the field. Radiologists should be aware about the radiological appearance of osteonecrosis as well as other bone complications and can differentiate bone metastasis to avert improper treatment.

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