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## Case Report

# Radiation-induced insufficiency fracture of the femur 18 years after radiation therapy

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## ARTICLE INFO

## Article history:

Received 19 October 2018

Accepted 26 October 2018

Available online 6 November 2018

## Keywords:

Radiotherapy

Musculoskeletal

Femur

Insufficiency

Fracture

Bone

Radiation-induced

Osteonecrosis

## ABSTRACT

Advances in oncologic treatment have improved survival rates, allowing late effects of radiotherapy to become more prevalent. Our patient, an 82-year-old woman with a remote history of right thigh basal cell carcinoma treated with resection and radiation therapy 18 years prior, presented with severe right thigh pain and inability to bear weight as she had suffered a femur fracture after a fall from standing. Initial imaging was suspicious for pathologic fracture secondary to malignancy due to imaging findings and because radiation-induced fractures have rarely been reported beyond 44 months from treatment. However, upon further imaging, evidence pointed to radiation-induced osteonecrosis as the mechanism for her insufficiency fracture. This case highlights the permanent deleterious effects of radiation therapy on bone, and the prudence of considering radiation-induced osteonecrosis as a mechanism of injury in low-energy trauma even long after radiation therapy. In addition, the case serves to review the natural history of irradiated bone injury and pertinent imaging findings.

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## Introduction

Insufficiency fracture (IF) is a subtype of stress fracture whereby fracture occurs from normal or physiologic stress applied to a weakened bone. Conditions such as osteoporosis, Paget's disease, hyperparathyroidism, chronic steroid use, and rheumatoid arthritis all weaken bone and predispose to IFs. Radiation exposure has increasingly been identified as a cause for IF, as studies have reported the development of IF after radiation for gynecologic, anal, rectal, and prostate cancer

[1]. Previously, this condition had been regarded as a rare occurrence. Earlier case studies have estimated cumulative incidences of symptomatic IF at 5 years after radiation treatment to be 6.8% in prostate [1], 8.2% in cervical, 11.2% in rectal, and 14.0% in anal cancer [2]. As the population over 65 is expected to almost double by the year 2050, and survival of cancers treated with radiation continues to increase, the number of insufficiency fractures will be expected to rise accordingly [3,4]. Already, more recent studies have reported a relative rise in radiation-induced pelvic IF with cumulative incidences at approximately 32%-36.9% at 2 years [5–7] and 45.2% [8] at 5 years.

Competing Interests: The authors declare that they have no conflicts of interest.

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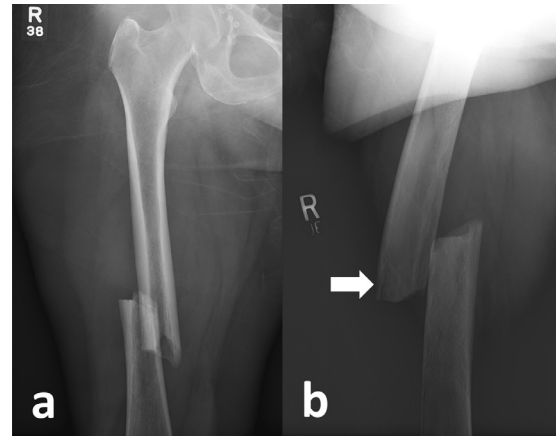
Radiation-induced IFs of the femur are significantly less frequent than radiation-induced pelvic IFs. When they do occur, it is most commonly either the femoral head or neck, however, the incidence is less than 1% of patients that undergo pelvic radiation therapy [9,10]. Radiation-induced fracture of the diaphyseal region of the femur is rarer still, and this case serves as the first well-described case of femoral diaphysis insufficiency fracture in the literature. Even more striking is the prolonged latency after the initial radiation therapy. This case demonstrates that radiation-induced IFs can occur well beyond the previously regarded window of 5-44 months [11] in which radiation-induced IFs typically occur. There may be mounting evidence that patients are at risk for radiation-induced fractures for the extent of their life after treatment, and therefore, this case adds new knowledge and highlights important aspects in the diagnosis and management of this condition.

### Case report

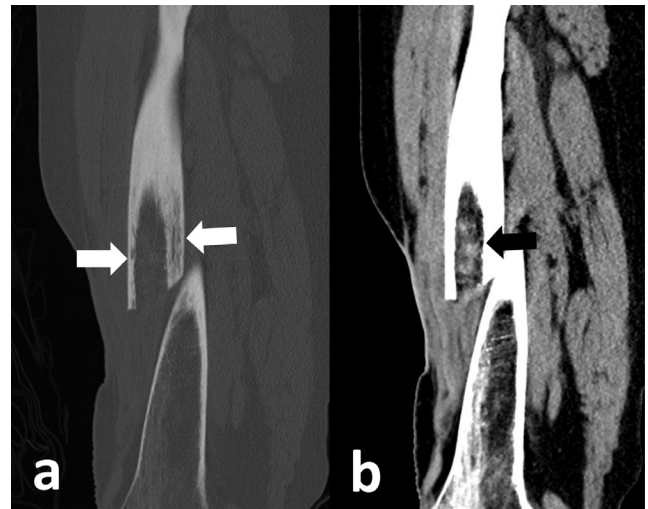
An 82-year-old Caucasian female with history of an anterior right thigh basal cell carcinoma treated with resection and radiation therapy 18 years prior presents with acute right thigh pain and inability to bear weight after a fall from standing in her home. The patient reported gradually worsening right thigh pain over the preceding 2 weeks that had progressed to the point she required a walker to ambulate around her home. The patient slipped while using the walker and fell from standing, landing on her right side. The patient had immediate severe pain localized to the right thigh along with inability to bear weight. Upon presenting to the emergency center, the patient's right thigh was swollen with obvious shortening of the right lower extremity. The patient was focally tender in the right thigh on palpation. There was no discoloration of the right lower extremity, and the right lower extremity was neurovascularly intact.

Radiographs of the right femur were obtained (Fig. 1), which showed a displaced oblique fracture through the mid femur diaphysis with subtle cortical tunneling on the lateral projections. Due to the low-energy mechanism of injury and the subtle cortical tunneling, further imaging evaluation was performed for possible underlying malignancy resulting in pathologic fracture. A noncontrast computed tomography (CT) of the right femur was performed (Fig. 2). Cortical tunneling could again be appreciated at the level of the diaphyseal fracture (Fig. 2A). Mixed soft tissue and fat attenuation was present within the medullary cavity at the fracture site (Fig. 2B). There was no periosteal reaction or soft tissue mass identified on CT. A large chronic superficial soft tissue defect could be seen on CT in the anterior thigh at the level of the femur fracture (Fig. 2), which corresponded to the resection site of the patient's prior basal cell carcinoma.

A noncontrast magnetic resonance imaging (MRI) of the right femur was performed in conjunction with the CT (Fig. 3). On T1-weighted sequences (Figs. 3A and B), patchy geographic areas of signal isointense to mildly hyperintense to skeletal muscle were present in the femur diaphysis proximal to the fracture. These areas were thought to represent areas of osteonecrosis related to prior radiotherapy. Of note, the



**Fig. 1 – 82-year-old with radiation-induced insufficiency fracture of the right femur. Presenting radiographs. Anteroposterior view (A) showing lateral displacement of the right diaphyseal fracture. Lateral view (B) showing posterior displacement with cortical tunneling noted (white arrow).**



**Fig. 2 – 82-year-old with radiation-induced insufficiency fracture of the right femur. Noncontrast CT at time of presentation. Bone window (A) shown demonstrates further evidence of cortical tunneling at the level of the diaphyseal fracture (white arrows). Soft tissue window (B) allows for appreciation of mixed soft tissue and fat attenuation present in the medullary cavity at the level of the diaphyseal fracture (black arrow). Note that there is no soft tissue mass or periosteal reaction. Additionally, a chronic superficial soft tissue defect can be seen in the anterior thigh at the level of the femur fracture, corresponding to prior resection site.**

left femur was included in the field-of-view on the coronal sequences and demonstrated complete homogeneous fatty marrow signal in the medullary cavity. On Short TI Inversion Recovery (STIR) sequences (Figs. 3C and D), mild diffuse increased signal was present throughout the right femur diaphysis. Soft tissue edema was seen surrounding the femur



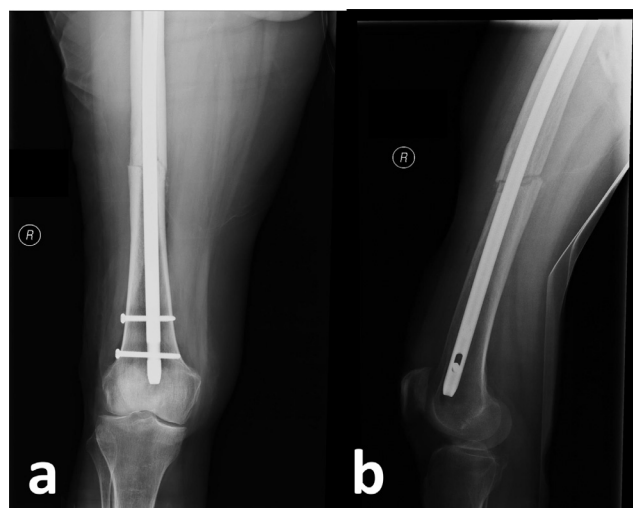
**Fig. 3** – 82-year-old with radiation-induced insufficiency fracture of the right femur. Noncontrast MRI. T1-weighted sequences (A and B) demonstrate patchy geographic areas of signal isointense to mildly hyperintense to skeletal muscle present in the femur diaphysis proximal to the fracture (white arrows). Short TI Inversion Recovery sequences (C and D) demonstrate mild diffuse increased signal throughout the right femur diaphysis.

fracture site. However, no intramedullary or soft tissue mass was identified on MRI.

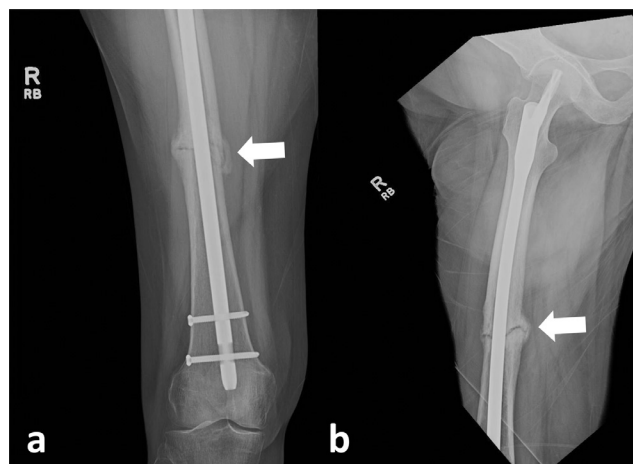
The patient subsequently underwent closed reduction with internal fixation using an intramedullary nail (Fig. 4). No biopsy was performed at the time of fracture fixation. The patient was discharged from the hospital with instructions for physical therapy along with vitamin D and calcium oral supplements. The patient responded well to treatment with partial healing of the femur fracture on 10-week follow-up radiographs (Fig. 5).

## Discussion

The imaging findings of radiation-induced osteonecrosis are pertinent to radiologists and clinicians alike as they can distinguish radiation-induced changes from metastatic disease, which often present in similar clinical contexts. In our case, the patient's low-energy mechanism of injury, history of malignancy, and cortical tunneling made the treating team highly-suspicious of pathologic fracture due to either local malignancy recurrence or a secondary cancer. In radiation-induced insufficiency fractures, the bone changes will be confined to the field of treatment [12]. An excellent example of this can be seen in Figure 2B as the radiation field and resection zone can easily be seen by the loss of subcutaneous tissue at the level of fracture. Furthermore, bone infarcts seen on MRI



**Fig. 4** – 82-year-old with radiation-induced insufficiency fracture of the right femur. Initial radiographs after closed reduction and cephalomedullary nailing of the right femur. The anteroposterior view (A) and Lateral view (B) both shows satisfactory reduction and alignment.



**Fig. 5** – 82-year-old with radiation-induced insufficiency fracture of the right femur. Radiographs 10-weeks post closed reduction and internal fixation. Anteroposterior view (A) and Lateral view (B) show only mild callus formation at the fracture site that has failed to bridge the cortical gap (white arrow).

are only present in the right femur, and not in the contralateral femur. For this reason, radiation-induced fracture was favored over osteoporosis. Although a consideration in a woman of this age, the musculoskeletal oncologist, radiologist, and orthopedic surgeon were all in agreement on etiology. Additionally, radiation-induced osteosarcoma, metastatic disease, or sarcoma are potential causes given her history, but were dismissed based on the lack of soft-tissue or bone-adherent mass on CT and MRI. Another possible cause of fracture that



should be addressed based on the location in this case, is an atypical femur fracture, which has been reported after prolonged bisphosphonate usage [13]. However, this patient does not have the hallmark radiologic findings such as lateral cortex “beaking,” or a medial spike [14]; nor does she have a history of taking bisphosphonates, making this mechanism of fracture implausible. Differentiating between malignancy and IF can be a difficult task; however, recent studies have shown that imaging properties can be used to indicate the appropriate diagnosis.

MRI and bone scintigraphy are both highly sensitive for detecting IF. Bone scintigraphy will show increased uptake in the area of fracture due to bone-remodeling; however, it is nonspecific, relatively cumbersome, and has lower sensitivity compared to MRI, especially since bone metabolism will be reduced in patients that have undergone chemotherapy and/or radiation [15,16]. MRI has also been shown to have superior sensitivity for the detection of IF (98% vs 53%) and soft tissue mass (99% vs 12.6%) as compared to CT [16]. In areas where red marrow is normally still present (ie, pelvis, vertebrae, and epiphyseal region of long bones), MRI will show high signal on T1-weighted images and low signal on STIR due to fatty infiltration of marrow, except in the first 2 weeks postradiation while reactive marrow changes are still occurring [11,17]. Evidence of IF after this point will show reversal of signal with a linear area of low signal on T1, high signal on T2-weighted and STIR images as well as notable fracture lines that can be visualized on contrast-enhanced T1-weighted images [8,11]. MRI has proven to be the best test for diagnosis of occult IF and useful in ruling out malignancy as a potential cause. Despite the cost of MRI and CT, it is important to swiftly rule out malignancy so that inappropriate treatment is not administered, the fracture can be treated promptly, and complications from prolonged immobility (ie, deep vein thrombosis and/or pulmonary embolism, loss of strength, decreased cardiac output, etc.) [16] are avoided.

The rarity of the type of fracture described along with the prolonged latency from radiation suggests that there are lasting effects of radiation therapy that leave bone permanently predisposed to insufficiency fractures. In skeletally mature patients, radiation has a direct, immediate effect on the function of osteoblasts, decreasing their overall number, and results in decreased matrix production. Studies evaluating the effects of radiation on osteoclasts show an imbalance in the number and activity of osteoclasts to osteoblasts, favoring bone destruction [18]. The cortical tunneling seen on radiograph and CT is a discernible manifestation of such changes as the osteoclasts resorb cortex along the axis of the bone.

Radiation also damages the integrity of blood vessels supplying the bone, increasing endothelial cell permeability which leads to perivascular edema, hemorrhage, and ultimately decreased perfusion. Over time, the irritation leads to intimal fibrosis and hyalinization of the tunica media, resulting in luminal narrowing and eventual obliterative endarteritis [18,19]. This causes microinfarcts, which can be seen on MRI as focal bone marrow hyperintensity, often surrounded by a geographic, low-signal intensity rim [20]. The resultant bone infarcts weaken the irradiated bone and increase susceptibility to IFs. In the case presented, these pathognomonic lesions were seen unilaterally in the radiation-treated femur directly

adjacent to the site of fracture, further making the argument for a radiation-induced mechanism of injury.

Hematopoietic stem cells are another component of bone that is exquisitely radiosensitive. Extensive damage can result in myeloid depletion and poor fracture healing secondary to inadequate blood supply and nonfunctioning osteoblasts [21]. The healing delay in the present case can be noted in Figure 5 with prominent callus formation, yet the fracture site has failed to bridge the cortical gap. A study by Cao et al. beautifully demonstrates the importance of the stem cell microenvironment with regard to their ability to regenerate postradiation. Damaging the microvasculature of the bone can lead to an irreversibly barren microenvironment where hematopoietic stem cells cannot recover, leading to refractory bony injury as bone remodeling is severely diminished [22]. Recovery is usually dose-dependent with reversibility under 30 Gy and irreversibility over 50 Gy [23]. Therefore, despite a satisfactory closed reduction with cephalomedullary nail fixation, the bone has a high probability to progress to nonunion with the presumed irreversible depletion of stem cells and osteoblasts secondary to radiation.

Deterministic effects of radiation occur once a particular threshold level is met and severity is proportional to increasing dose beyond that point. Presently, insufficiency fracture is not a well-regarded deterministic effect of radiation; however, multiple studies have independently found approximately 50 Gy to be a significant predisposing factor to the development of IF [11,24]. This corroborates the previously reported biochemical threshold for radiation-induced changes in bone at 30 Gy, with cell death and devascularization of bone occurring at doses over 50 Gy [19]. The relevance of this threshold is important as standard radiation treatments for cancer can easily exceed 50 Gy, but may be tailored to better avoid these complications in the future.

The timing of the fracture is another key piece that demonstrates how bone may be permanently damaged by radiation therapy. Although this is the first radiation-induced femur fracture described after such a long latent period, isolated cases of latent fractures involving other regions have been mentioned in the literature. One review touches on a case of osteoradionecrosis of the chest wall 30 years postradiation, and a pelvic fracture 32 years postradiation [19]. Clinicians and researchers are conducting longer follow-up studies which may reveal this likely under-reported complication. More prospective studies with robust follow-up are needed at this time to further delineate the prolonged effects of radiation therapy on bone.

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