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Osteoradionecrosis of the Ribs following Breast Radiotherapy

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Key Words

Breast radiotherapy · Rib fracture · Osteoradionecrosis

Abstract

Introduction: Osteoradionecrosis (ORN) of the chest wall is a rare complication after whole-breast radiotherapy (RT). Herein, we report a case of ORN involving the underlying ribs following adjuvant whole-breast RT using standard fractionation and conduct a review of the literature. **Case Report:** A previously well 43-year-old female with right-sided, early-stage, node-negative breast cancer was treated with breast-conserving surgery. She subsequently underwent adjuvant whole-breast RT receiving 50 Gy in 25 fractions over 5 weeks using standard tangential photon fields with 6 MV photons followed by an electron boost of 10 Gy in 5 fractions according to International Commission on Radiation Units (ICRU) requirements. Eleven months after RT, the patient developed right lateral chest wall pain, with magnetic resonance imaging (MRI) demonstrating two fractures involving the underlying right fifth and sixth ribs associated with fatty marrow changes in the second to sixth ribs, thus raising the possibility of ORN. Treatments including hyperbaric oxygen, pentoxifylline and vitamin E were used with symptomatic improvements. There was demonstrable resolution on follow-up MRI at 2.5 years. **Conclusion:** The incidence of ORN utilising modern RT techniques and standard fractionation is rare. Numerous treatments are available, with variable response rates. Emerging evidence of predictive gene profiling to estimate the risk of radiation sensitivity may assist in individualising preventative strategies to mitigate the risk of ORN.

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Introduction

The addition of whole-breast radiation therapy (RT) to lumpectomy significantly reduces local recurrence and imparts a long-term survival benefit [1]. Several late RT toxicities attributable to whole-breast RT include lymphoedema, skin changes, breast fibrosis, brachial plexopathy, tissue necrosis, pneumonitis, pericarditis and secondary malignancies [2]. Radiation-induced rib fracture (RIRF) is a very rare, late complication following conventionally fractionated RT for breast and lung cancers with a reported incidence between 0.1 and 5% [2, 3]. Various patient, tumour and treatment factors are attributable in cases of RIRF following whole-breast RT.

The management of RIRF involves optimising analgesia, excluding recurrent disease and trialling established treatments for osteoradionecrosis (ORN). The majority of RIRF resolve spontaneously without intervention [4]. ORN is characterised by radiation-induced ischaemic necrosis of bone, with or without associated soft tissue necrosis. It is a diagnosis of exclusion when fractures within an RT field fail to heal following conservative treatment. A distinction between RIRF and ORN is needed to adapt treatment accordingly.

Herein, we report a case of ORN affecting the ribs following adjuvant whole-breast RT, postulate the potential contributing factors and conduct a review of the literature on ORN following breast RT.

Case Report

A previously well 43-year-old lady presented with bloody discharge from her right nipple. A bilateral mammogram and ultrasound demonstrated a solitary hypodense lesion within the inferior portion of her right breast. Fine-needle aspiration was suspicious for carcinoma. She underwent wide local excision and sentinel lymph node biopsy which revealed a 3.5-mm grade 1 invasive ductal carcinoma with associated intermediate-grade ductal carcinoma in situ. The tumour was hormone receptor (ER/PR) positive and HER2 negative. The closest margin was 1.7 mm posteriorly. Sentinel lymph node biopsy was negative, so she was staged pT1aN0M0.

The patient had no other significant medical co-morbidities. She was physically very fit and slim in keeping with her occupation as a dancer. The oral contraceptive pill which she was taking prior to diagnosis was ceased. Her mother had previously been treated for ductal carcinoma in situ at age 45 years.

Adjuvant whole-breast RT was recommended to reduce the risk of local recurrence. No hormone therapy was recommended due to the small primary lesion size, low-grade histology and node negativity. She received 50 Gy in 25 daily fractions over 5 weeks using standard tangential 6 MV photon fields to the whole breast, followed by an electron boost of 10 Gy in 5 fractions to the surgical cavity. Treatment was in accordance with International Commission on Radiation Units (ICRU) requirements with acceptable planning target volume coverage, homogeneity and dose to organs at risk. The maximum dose to her whole breast was <105% of the prescription dose. Daily monitor units were retrospectively reviewed to ensure correct treatment delivery.

A moderate (grade 2) radiation dermatitis developed during treatment, which resolved soon after completion of RT. In addition, a small (1.5-cm) area of cellulitis developed over the inferolateral portion of her right breast 1 month after treatment, which was treated with flucloxacillin and resolved completely.

Eleven months after RT, the patient developed severe right-sided lateral chest wall pain which was pleuritic in nature. Chest radiography was normal. A bone scan showed features consistent with costochondritis, but no evidence of metastatic disease. A computerised axial tomography (CT) pulmonary angiogram showed no evidence of pulmonary embolus, rib fracture or metastatic disease. Four months later, the patient developed intractable pain in the right chest wall upon minimal exertion. Repeat CT chest imaging demonstrated a healing fracture involving the right sixth rib (fig. 1) and features consistent with a fracture of the right anterior second rib without evidence of bony destruction. Magnetic resonance imaging (MRI) was performed to ascertain aetiology, which confirmed fractures of the right fifth and sixth ribs. There was fatty marrow replacement involving the right second to sixth ribs consistent with radiation changes (fig. 2). Repeat bone scan revealed mildly increased uptake in the right second, third, fifth and sixth ribs.

Investigations to rule out contributing factors including serum calcium, renal function, haematology, C-reactive protein, vitamin D, parathyroid hormone, thyroid function, bone mineral density and myeloma screen were within normal limits. Radiation ORN was determined as the most likely cause of the rib fractures. The patient commenced treatment with pentoxifylline, vitamin E and hyperbaric oxygen therapy. She declined clodronate treatment in view of the small risk of mandibular necrosis. There was no demonstrable improvement in symptomatology or radiological re-evaluation after 6 months of therapy.

Two years after her presentation with chest wall pain, a progress CT scan showed a non-united fracture involving the anterolateral aspect of the right fifth rib with localised sclerosis and a partially united fracture of the anterior aspect of the sixth rib at the costochondral junction. The previously demonstrated changes involving the right anterior second and third ribs had resolved. A repeat MRI scan performed 2.5 years after initial chest wall pain confirmed two areas of signal abnormality, which corresponded to the persistent non-united fractures on the CT scan 6 months prior, with a degree of sclerosis on T1 imaging and hyperintensity on T2 imaging (fig. 3). There was no generalised bony abnormality or MRI features of widespread ORN.

Over the 2.5-year follow-up period, the patient's anterior second rib pain settled, and her right lateral rib pain improved without the need for narcotics or anaesthetic nerve blocks. Physical examination revealed progressive right breast shrinkage in keeping with RT-induced fibrosis. The patient's quality of life was negatively impacted, resulting in the modification of her active lifestyle with avoidance of all upper body exercises. As a result, she stopped professional dancing and became a dance teacher.

Discussion

We report a rare late RT complication in a 43-year-old woman undergoing standard whole-breast RT after breast-conserving surgery. No contributing factors were identified on investigation to exclude non-malignant or treatment-related conditions. Radiological and clinical findings were consistent with radiation-induced ORN, leading to non-pathological fractures.

The risk of an RT-induced rib fracture following standard whole-breast RT is low, with published series [2] reporting rates between 0.3 to 1.8%, translating to 1–3 cases per 1,000 patients treated using modern RT techniques [5]. Patients with ORN can present with diverse symptomatology, ranging from occult disease to major bone destruction with soft tissue necrosis, months to years after RT [6]. Severe ORN of the ribs is exceedingly rare, with only a handful of published case reports over the past 10 years [7]. Whilst rib ORN is rare,

ORN of the mandible is relatively more common owing to the higher doses delivered for head and neck cancers and the poor vascular framework of mandibular bone [8]. Risk factors which have been implicated in mandibular ORN include higher T stage, tumour infiltration of the adjacent bone, RT modality and previous surgery [9].

No universally accepted treatment exists for ORN [10]. The RT-induced fibroatrophic process, initiated by chronic inflammation and potentiated by tumour necrosis factor- α has been proposed as the biologic explanation for ORN [10]. Various therapies have been developed aimed at inhibiting tumour necrosis factor- α in this context, with one such regime comprising pentoxifylline, vitamin E and clodronate [6]. A proportion of patients treated with this combination regimen have resulted in both clinical and radiological regression. Hyperbaric oxygen has long been proposed as an adjunctive treatment in patients with late RT-induced tissue injury and may be associated with improved outcomes [11]. Surgical approaches including debridement with chest wall reconstruction are generally reserved for patients who fail conservative medical treatments [12].

Our patient developed grade 2 radiation dermatitis. However, moderately severe acute RT side effects do not necessarily predict late side effects. The consequential late effect phenomenon is often associated with severe (grade 3–4) acute RT reactions [13], which was not observed in this case. We postulate, given the extent of the patient's breast fibrosis, that an underlying genetic or biological predisposition to RT sensitivity may have played a role in the development of ORN and the subsequent fracture. There are several known genes which have been identified as potential predictors for RT-induced fibrosis [14]. Advice was sought from clinical genetics ruling out known radiation sensitivity syndromes. Other investigators have established a correlation between various inherited genetic variations in the form of single nucleotide polymorphisms and the degree of differing radiation sensitivity [15], but these tests are not clinically available. Larger confirmatory genome-wide association studies are required to confirm these results and validate the use of gene profiles as predictive and prognostic biomarkers for RT sensitivity.

Conclusion

We report a case of ORN and a fracture of underlying ribs after adjuvant whole-breast RT following breast-conserving surgery, highlighting this uncommon complication using modern RT techniques. Various treatment options are used with variable response rates. Emerging evidence of predictive gene profiling to estimate the risk of radiation sensitivity may assist in further individualising treatment recommendations.

Statement of Ethics

The authors have no ethical conflicts to disclose as the patient was treated on a standard protocol, and all information was de-identified.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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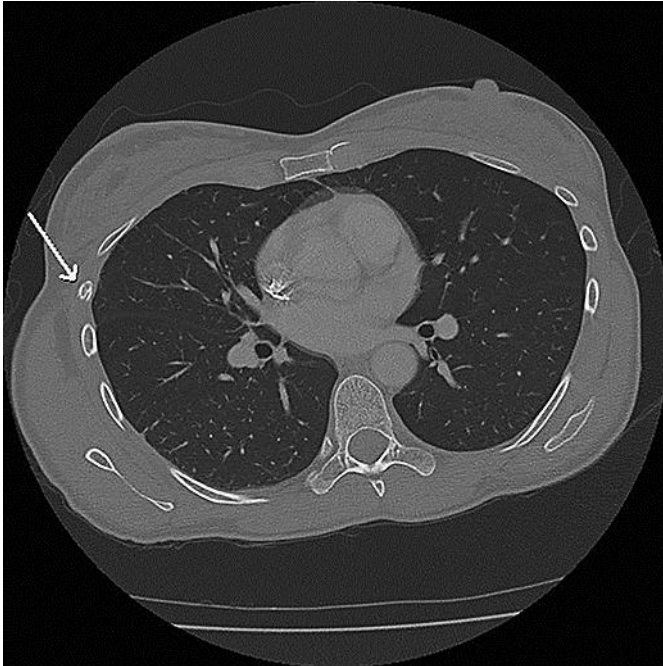


Fig. 1. CT chest confirming a healing right second rib fracture (arrow). There is no evidence of bony destruction.



Fig. 2. T1-weighted MRI of the chest revealing fatty marrow replacement of the right sixth rib.

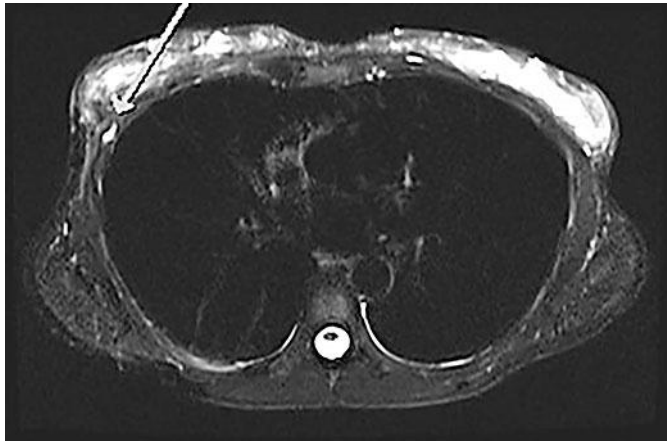


Fig. 3. Chest MRI 2.5 years after presentation showing hyperintensity on T2-weighted imaging corresponding to a persistent non-united fracture (arrow).