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Case Report

Diagnosing sacral insufficiency fractures after radiotherapy in women with cervical cancer: Report of three cases

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ABSTRACT

Introduction: Diagnosing sacral insufficiency fractures (SIF) in oncology patients is a challenge to radiologists, and recognition of imaging features is essential in order to avoid misdiagnosis of bone metastases and prevent patients from inaccurate treatment.

Clinical cases: in order to better understand the essence of this pathology and to make diagnosis easier, we present three clinical cases of SIF in patients with cervical cancer. All patients received radiation therapy (external beam radiation and brachytherapy) and chemotherapy with cisplatin. Patients underwent pelvic MRI, CT, SPECT or SPECT/CT examinations. One patient underwent a FDG-PET/CT examination.

Conclusions: SPECT/CT should be included in the differential diagnostics when radiological features of pelvic bone pathology on CT or MRI are undetermined or SIF are suspected. SIF must always be considered in oncology patients with pelvic pain, especially in postmenopausal state and after radiation therapy. For patients with osteoporosis, bone density screening and precise review of the most common fracture sites are recommended.

Introduction

Sacral insufficiency fractures (SIF) are a type of bone fracture that occurs from normal physiological stress on the bone that is not sufficiently resilient to elasticity. SIF usually develops in patients with osteoporosis, osteomalacia, primary hyperparathyroidism, rheumatoid arthritis, and Paget's disease, while taking corticosteroids or after pelvic radiation therapy (RT) [1]. Several studies have shown that the incidence of insufficiency fractures in risk group patients ranges from 9.5% to 11.4% [2], and among the elderly from 1% to 5% [3]. In order to prevent inappropriate and excessive treatment, SIF must be distinguished from bone metastases in patients with oncological diseases.

A comprehensive understanding of the pathophysiology associated with the effects of radiation on bone is still unclear. Important factors include age, menopausal status, and genetic factors that increase the risk of fractures [4]. There is evidence that radiation causes bone matrix damage, increases

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bone marrow fat degeneration, and reduces bone vascularization, which contributes to the direct effects of radiotherapy on bone function and strength [5,6].

The clinical signs of sacral insufficiency fractures are not specific and usually include pain that is difficult to localize in the pelvis, lower back, buttocks or legs, as well as limited movement and daily dysfunction. In some cases, the clinic signs may not appear at all. Symptoms may occur after an inadequately low-energy injury, although most patients deny the injury [7]. Symptoms worsen during exercise and are relieved at rest, especially when lying on your back. The diagnosis of fracture is also complicated by the fact that exacerbations of concomitant pathology, such as spinal canal stenosis, lumbar radiculopathy, or osteoarthritis, may be mistaken for sudden lower back pain onset. As a result, radiological diagnosis is often given late, sometimes weeks or months after the fracture. Pelvic pain after RT is common and raises concerns about tumor recurrence or metastatic disease in patients with oncological disease [8]. In addition, SIF can often be interpreted as malignancies in radiological studies [9].

SIF can occur as early as 2 months after RT, but can appear 8 years or even later, with a median duration of 6 to 20 months [10]. The majority of patients receive conservative treatment, including resting, immobilization, and analgesia, but unstable pelvic fractures should be treated surgically [11].

Misdiagnosis can lead to unnecessary and expensive diagnostic tests and chemotherapy, and late diagnosis and treatment of SIF can cause mobility disorders and complications [12]. Therefore it is necessary to know radiological and clinical signs of SIF and seek appropriate diagnostic methods to solve this problem. We present three clinical cases in which female patients received radiation treatment to the cervix and subsequently developed pelvic insufficiency fractures.

Case presentation

Case 1

A 61 year-old-woman with IB stage cervical cancer complained of pelvic pain 9 months after chemotherapy and radiotherapy. The patient was treated with 46Gy external beam radiation (EBR) in 23 fractions following 15Gy brachytherapy (BT) in 3 fractions. The patient also received cisplatin (total 350mg in 5 cycles). Pelvic MRI was performed, the signal in sacrum region was altered (more on the left side), hypointensive signal zones were visible in sacrum in T1 and T2 sequences with contrast material accumulation and hyperintense signal zones in the STIR sequence without clear fracture lines (Fig. 1). The pathology in MRI images were differentiated between bone metastases and post-radiation/inflammatory or post-traumatic changes.

1 month later, bone scintigraphy was performed to rule out bone metastases. Plain images showed a typical “Honda” or “H” sign (Fig. 2). SPECT/CT images revealed fracture lines in the left lateral side of the sacrum with osteosclerosis and increased Tc-99m MDP uptake – the changes were interpreted as insufficiency fractures. The diagnosis was confirmed by following radiological examinations and by changes of clinical signs.

Case 2

A 52-year-old woman diagnosed with IIB stage cervical cancer was treated with 50,4Gy EBR in 28 fractions following 28Gy brachytherapy in 4 fractions and chemotherapy with cisplatin 1,8mg/week (total 310mg). 34 months later the patient presented with a complaint of low back pain radiating to both lower limbs. She was treated on analgesics, which did not alleviate the pain. Pelvic MRI was performed to look for disease progression. T1 and T2 sequences showed uneven hypointensive signal, contrast material accumulation zones (Fig. 3). Local inflammatory and post-radiation changes were differentiated with bone metastases. 1 month later, bone scintigraphy was performed. An atypical “H” sign (without a horizontal line) was visible on plain images (Fig. 3). The area of inhomogeneous sclerosis without visible fracture lines with intense accumulation of Tc-99m MDP was observed on SPECT/CT images – changes were interpreted as sacrum insufficiency fractures. The diagnosis was confirmed by following radiological examinations and by changes of clinical signs. In subsequent MRI scans, contrast material accumulation disappeared.

Case 3

A 66-year-old woman diagnosed with IIB stage cervical cancer was treated with 50,4Gy EBR to cervix, uterus and region lymph nodes in 28 fractions following 26Gy brachytherapy in 4 fractions and chemotherapy with cisplatin (total 420mg in 6 cycles). 12 months later, a pelvic MRI was performed for disease follow-up. The patient complained of pelvic pain for a few weeks.

T1 sequence showed hypointensive signal in left lateral sacrum side, contrast material accumulation was seen in this area (Fig. 4). These changes were interpreted as bone metastases. 1 month later, FDG PET/CT was performed. Examination showed active metabolic lesion in left sacrum side and smaller lesion in right sacrum side (Fig. 4). Lesions were interpreted as bone metastases. 6 months later, chest, abdomen and pelvis CT was performed for disease progression signs. Pathology in the sacrum was interpreted as possible mixed-type metastases. 5 months later, a pelvic MRI was performed, which showed decreased contrast material accumulation in the sacrum, other changes were similar as in previous examinations (Fig. 5). A few months later, a bone scintigraphy was performed. Tc-99m MDP accumulation was seen in the sacrum lateral sides with no evidence of bone metastases in other skeletal regions (Fig. 5). Combining SPECT, CT and MRI images, changes were interpreted as healing sacrum insufficiency fractures.

Discussion

Whole-body bone scintigraphy (WBS) is a sensitive examination method for the detection of SIF and it is often possible to see a typical characteristic “H” mark that is visible when

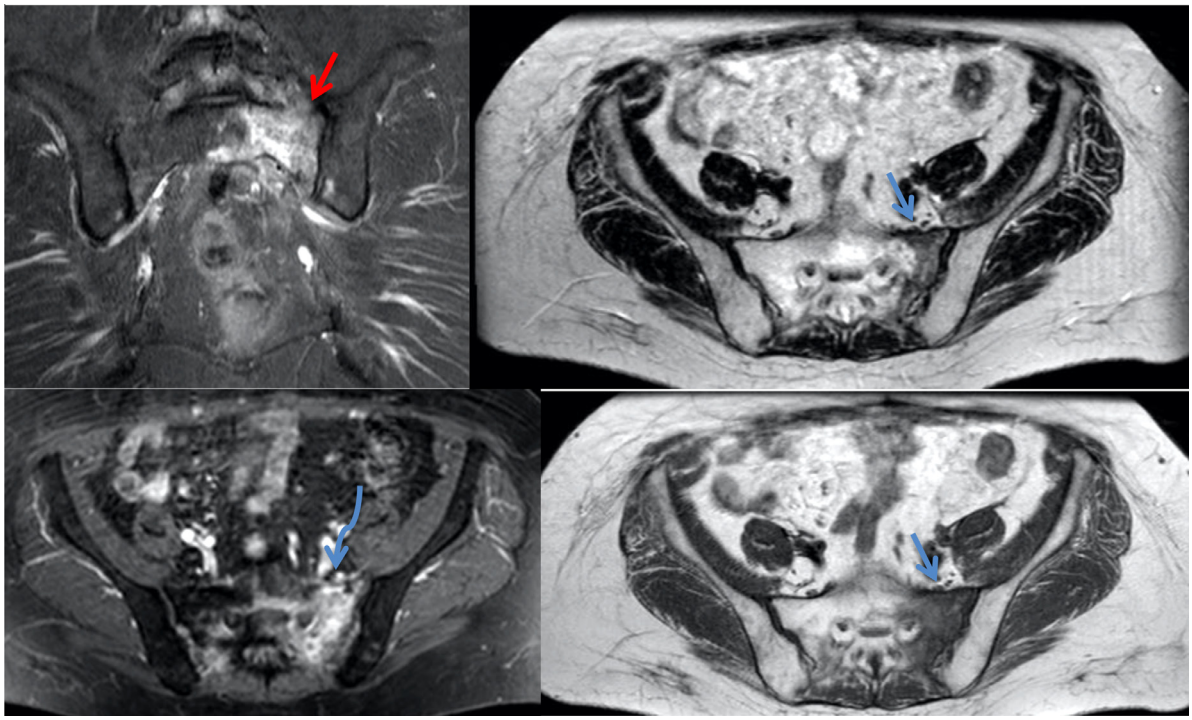

Fig. 1 – Case 1. Altered MRI signal zones in sacrum (more on the left side) in T1 and T2 sequences (straight blue arrows) with contrast material accumulation (curved blue arrow) and hyperintense signal zones in STIR sequence (red arrow). (Color version of figure is available online.)

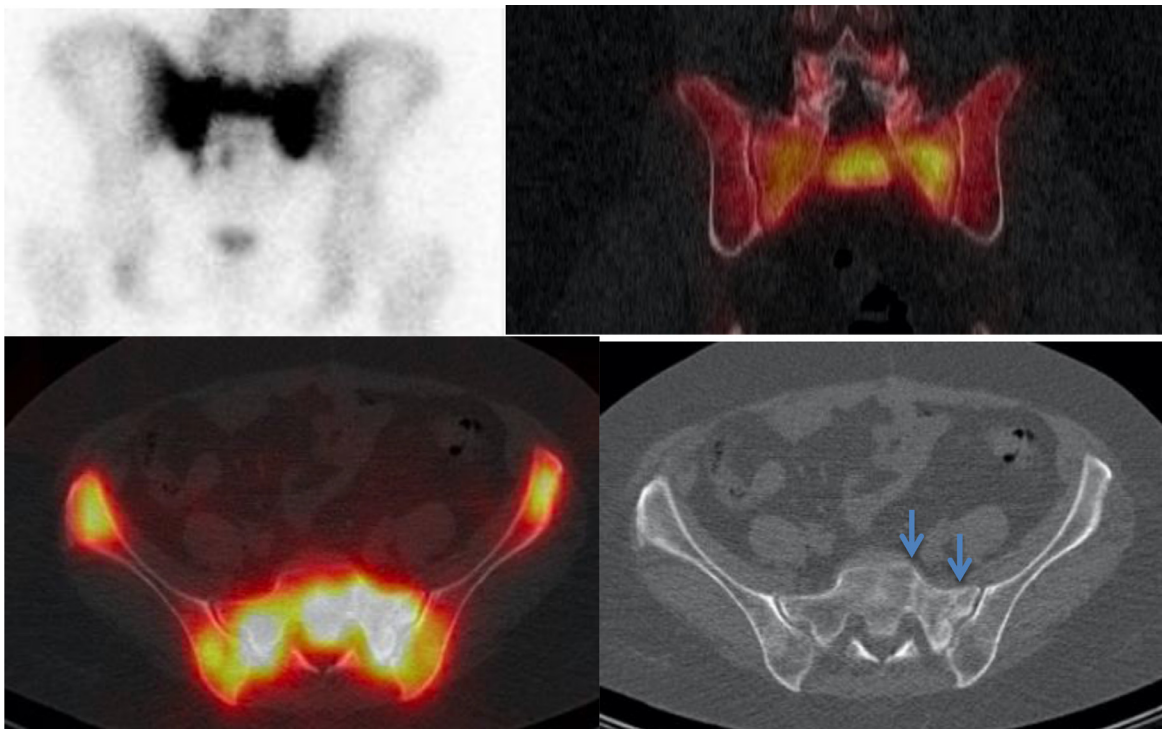

Fig. 2 – Case 1. Typical "H" sign is seen on planar bone scintigraphy and SPECT/CT images. On CT images fracture lines (blue arrows) and osteoclerosis with increased Tc-99m MDP uptake are seen in sacrum. (Color version of figure is available online.)

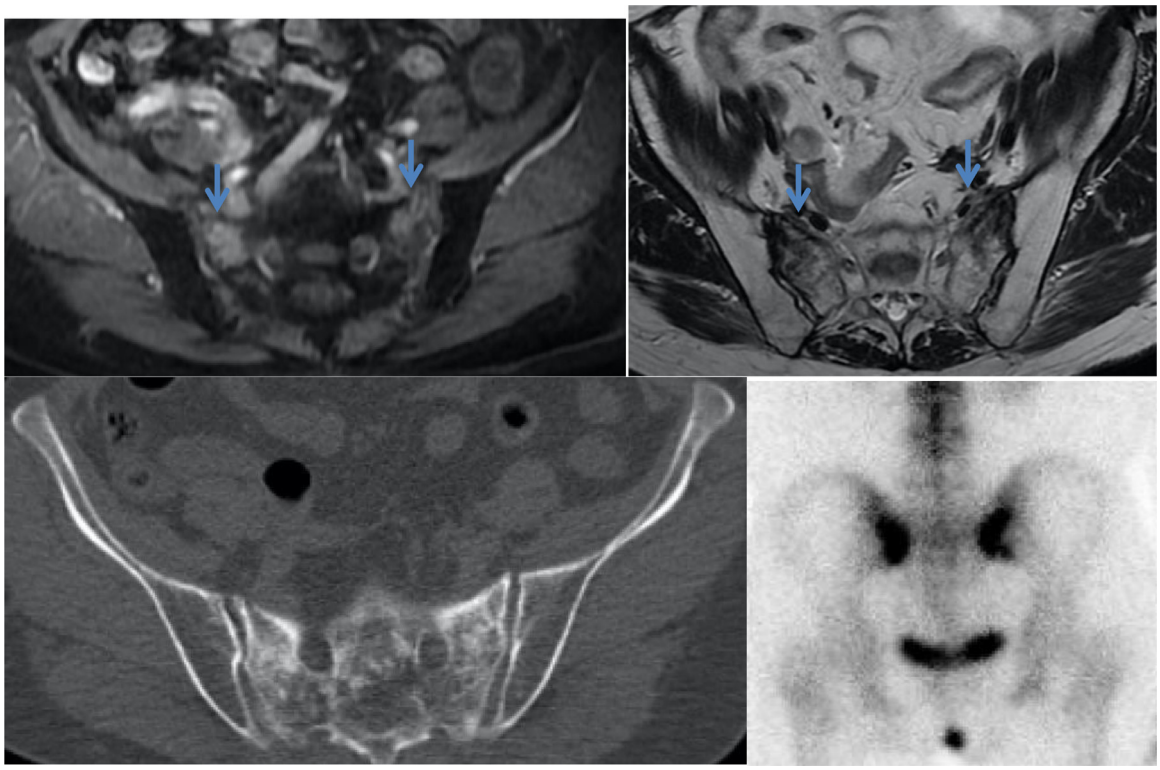

Fig. 3 – Case 2. Contrast material accumulation zones and uneven hypointense signal in T1 sequence on MRI images (blue arrows). Bone scintigraphy showed atypical "H" sign and inhomogenous osteosclerosis is seen on CT images. (Color version of figure is available online.)

fracture lines are in the lateral sides and central part of the sacrum. According to some studies, this sign is detected in 30%–40% of SIF cases [13,14]. When the typical "H" sign is not visible or when the patient has a history of oncological disease, these changes are less specific [15]. Bone metastases may be present with SIF, so the diagnosis of SIF cannot be made from WBS alone, therefore a SPECT/CT scan is performed to improve specificity.

There are few studies on the role of SPECT/CT in the diagnosis of SIF, especially after radiotherapy [16,17]. Diagnosis of SIF can be a challenge for a radiologist if he or she does not know and cannot properly assess the features of this pathology. 1 of the most common features of SIF are osteosclerosis and fracture lines in the areas of abnormal radiotracer uptake. Also, multiple fracture sites can be present in some cases, so caution must be taken when one fracture line is found [16]. In all3 of our cases SPECT/CT showed typical or atypical "H" sign with inhomogeneous osteosclerosis with or without fracture lines in the areas of increased Tc-99m MDP uptake. In addition, SIF manifest as new pain in the lumbar or pelvic area without any trauma and the lesions can be interpreted as bone metastases. Sudhir et al. conducted a study in which 2 patients complained of low back pain with radiation to both legs and underwent spinal canal decompression, but symptoms persisted after surgery [3]. Therefore, the authors concluded that sometimes SIF can be undiagnosed.

Our clinical cases showed that the use of SPECT/CT after CT and/or MRI studies, improved diagnostic accuracy in patients with suspected SIF. Determining the presence of bone metastases after RT has a significant impact on the patient's further treatment, particularly because it is associated with reduced survival [18]. Therefore, the use of SPECT/CT may help in earlier diagnosis and selection of appropriate treatment for patients with SIF. Moreover, by reducing the frequency of undetermined pathological changes and classifying them as non-malignant lesions, excessive treatment and other costly imaging techniques could be avoided. Also, if the patient is misdiagnosed or the diagnosis remains unclear, the person may need a biopsy, chemotherapy or additional RT to an already weak and damaged bone [17,19].

A biopsy was not performed on any of the patients we studied. Biopsy is not recommended due to the high possibility of fracture and low diagnostic value [20]. In addition, there is decreased vascularization in RT damaged bone marrow, which can lead to infection at the biopsy site and cause osteonecrosis. Clinical and radiological signs may confirm the diagnosis, as the clinical signs improves over time and the radiological signs regress, although it should be kept in mind that new fractures may occur in other areas as well.

An MRI scan has a high sensitivity for detecting early bone marrow edema [20]. Sacral bone marrow edema may be inhomogenous, with indistinct boundaries; in T1 it appears as a hypointensive signal, in STIR and T2 sequences as a hyperintensive signal. With bone marrow edema, fracture lines can also be seen, which occur between 3 weeks and 3 months and appear as a lower signal band, best seen in T1 contrast sequences [20]. The T1 hypointensive signal and the STIR hyperintensive signal may also be present in the presence of

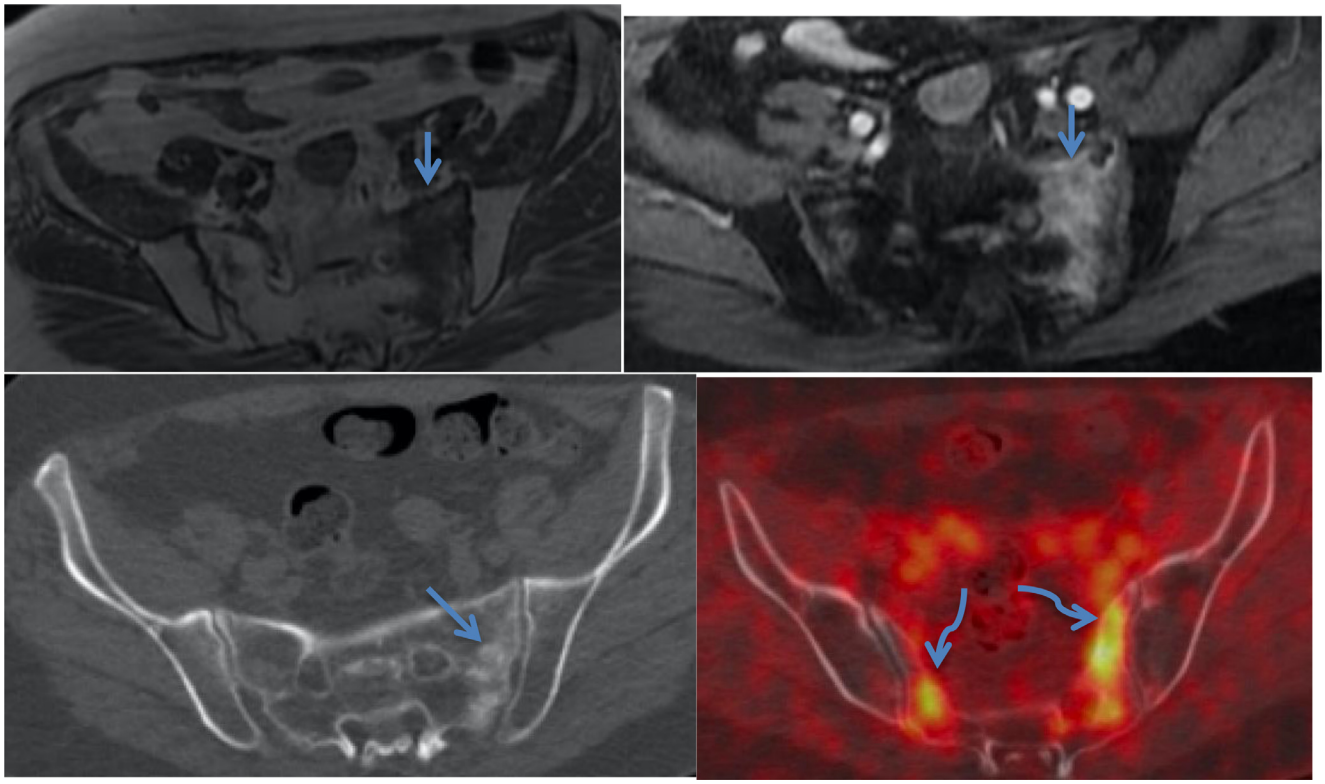

Fig. 4 – Case 3. Hypointense signal on T1 sequence and contrast material accumulation on left sacrum side (straight blue arrows). FDG-PET/CT showed active metabolic lesion in left sacrum side and smaller lesion in right sacrum side (curved blue arrows). Osteosclerotic areas are seen on CT images (straight blue arrow). (Color version of figure is available online.)

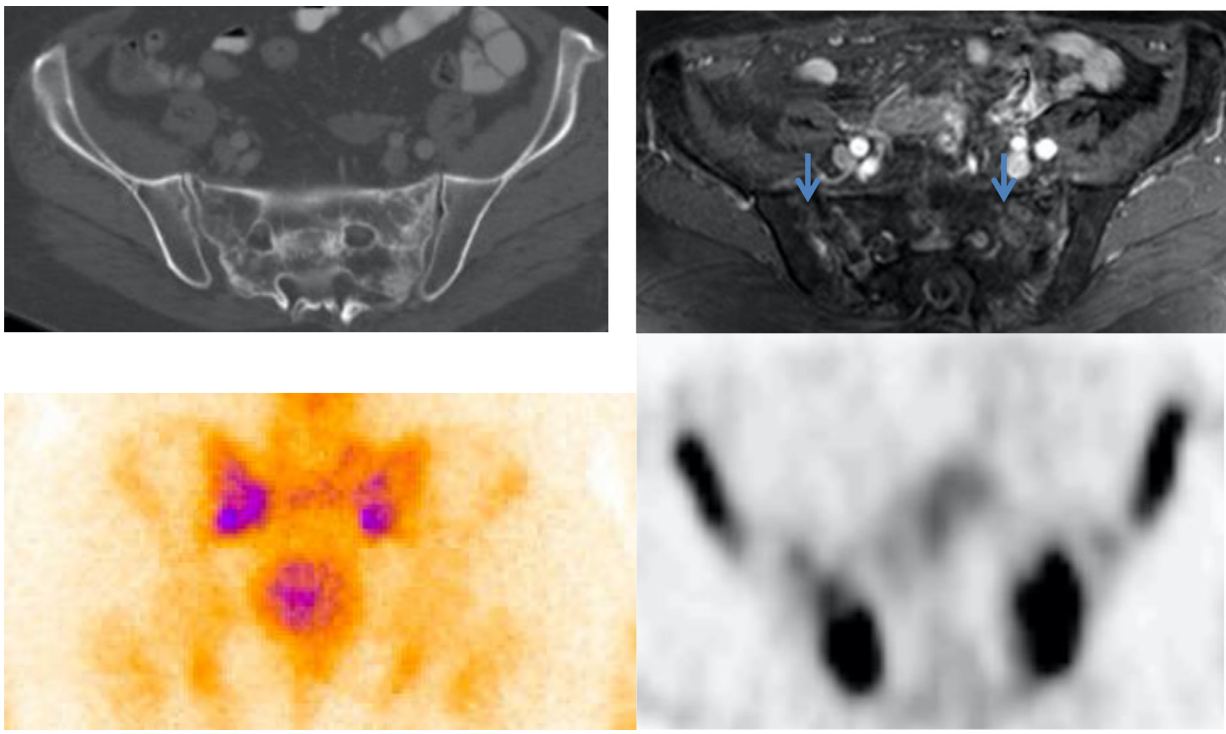

Fig. 5 – Case 3. Follow-up CT showed inhomogenous sclerosis without visible fracture lines. Follow-up MRI showed slightly increased contrast material accumulation in sacrum (blue arrows). Tc-99m MDP accumulation in sacrum lateral sides was seen on bone scan images. (Color version of figure is available online.)

metastases, but no fracture lines or contrast-enhanced focal lesions will be visible. Diagnosis of pathology may be more difficult when no clear fracture lines are visible and there is an accumulation of contrast material with indistinct boundaries; then, such changes are more difficult to distinguish from metastases.

Fatty degeneration of bone marrow, as seen in MRI scans, is a common consequence of RT [21]. Depending on the dose used, fatty bone marrow degeneration may be seen 10 to 14 days after RT. If RT doses are less than 30–40 Gy, the changes are reversible, but if doses are greater than 40 Gy, the changes are irreversible [22].

CT and MRI are widely used for the diagnosis of SIF. Cabbarus et al. compared the two methods for the determination of SIF [23]. 67 sacral fractures were evaluated and the sensitivity of MRI was 100% and that of CT was 74.6%. However, the ability of both examinations to identify fracture lines was similar (95.3% and 89.7%). According to some studies, the sensitivity of bone scintigraphy to detect SIF is 96% [15], and SPECT or SPECT/CT further increases both sensitivity and specificity [24].

Chemotherapy in gynecologic cancer patients is often used in combination with RT to increase tumor control, but chemotherapy is also thought to increase RT toxicity. However, several studies have shown that concomitant chemotherapy did not significantly affect the incidence of SIF [17]. The prevalence of pelvic insufficiency fractures was found to be not significantly higher in patients receiving chemotherapy (33/193, 17.1%) than in patients not receiving chemotherapy (67/317, 21.1%). In our clinical cases, all patients received chemotherapy in combination with RT.

In several studies, the estimated time after which SIF can occur due to radiotherapy ranges from 2 weeks to 190 months after treatment and is difficult to predict [25,26]. But it is important to note that not all SIF develops after RT. 1 of the most significant factors in the development of SIF is osteoporosis [27–29]. However, the assessment of bone mineral density (BMD) by dual-energy X-ray absorption scanning is not common, especially in patients with cervical cancer. In our study, all patients had a postmenopausal condition, so it could be assumed that most of them may have had osteoporosis, but there were no accurate data on BMD. Therefore, assessment of BMD is recommended in post-RT and postmenopausal patients, especially when SIF is suspected. Appropriate screening and possible treatment for osteoporosis could help reduce the incidence of SIF, especially after RT.

Conclusion

SIF should be suspected in patients with oncological gynecology diseases with new onset pelvic and/or lumbar pain, especially in the postmenopausal state or after radiation therapy. Moreover, determination of bone mineral density and radiological examination of the pelvic ring are recommended due to the high risk of fracture development in these areas. Also, a SPECT/CT scan should be performed when changes in pelvic bones on CT and/or MRI images are undetermined.

Patient Consent Statement

Images in our study are entirely anonymised from which the individual cannot be identified (MRI, CT, SPECT/CT and PET/CT images) and do not contain any identifying marks and are not accompanied by text that might identify the individual concerned.

Written informed consents for scientific purposes are obtained from patients, but they are in Lithuanian language. We can send it, if it's mandatory.

Declaration of Competing Interest

None.

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