Jpn J Radiol (2016) 34:771–778
DOI 10.1007/s11604-016-0585-8

PICTORIAL ESSAY

Clinical spectrum and diagnostic pitfalls of multiple abnormal uptakes on bone scintigraphy

Fumihiro Tsubaki[1] · Seiji Kurata[1] · Shuji Nagata[1] · Kiminori Fujimoto[1] · Toshi Abe[1]

Received: 7 July 2016 / Accepted: 15 September 2016 / Published online: 29 September 2016

Abstract Bone scintigraphy with technetium-99m (^{99m}Tc)-labeled diphosphonates is one of the most frequently performed radionuclide procedures. Accumulation of ^{99m}Tc-labeled diphosphonate is well recognized to reflect conditions of accelerated bone turnover and metabolism. Therefore, it is a functional imaging modality for detecting metastatic bone tumors, metabolic bone disease, traumatic injury, and inflammation. This pictorial essay describes the possible patterns of distribution of abnormal uptake for differential diagnosis of metastatic bone tumor, as well as the diagnostic pitfalls of bone scintigraphy.

Keywords Bone scintigraphy · Metastatic disease · Metabolic disorder

Introduction

Bone scintigraphy with Tc-99m labeled diphosphonates has been frequently used in searches for metastatic bone tumors. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for cancer staging or detection of recurrence has been covered by the health insurance in Japan; therefore, the number of bone scintigraphy procedures for evaluation of bone metastasis has been declining. On the other hand, bone scintigraphy is still often used to search for osteoblastic or mixed metastasis according to tissue-specific characteristics of the primary malignant tumor, such as prostate cancer and breast cancer. In general, the presence of multiple and randomly distributed foci of increased uptake of varying shapes is highly suggestive of metastatic bone tumor. Although multiple or diffuse increased uptakes may be encountered in metabolic bone disease, trauma, and inflammation, analysis of the pattern of distribution of the abnormalities can often distinguish metastatic disease from other entities [1]. Therefore, understanding the pattern of abnormal increased uptake on bone scintigraphy is recommended.

Metastatic disease

In general, abnormal increased uptake of bone lesions depends on the osteoblastic response, which is associated with bone destruction from the metastatic process [2]. Osteoblastic metastasis is most commonly found in patients with prostatic carcinoma (Fig. 1). Ovarian and gastric carcinoma may also give rise to osteoblastic bone metastasis, but at a lower frequency (Fig. 2). On occasion, extensive disease dissemination may be characterized by increased uptake throughout the entire skeleton, as well as faint uptake by the kidneys [3] (Fig. 3).

Results may be falsely negative in cases of aggressive metastases with insufficient osteoblastic response, intratrabecular metastases, or micrometastases. In such cases that have rapid destruction by the osteolytic process, bone scintigraphy would show "cold lesions" with absent uptake. A rim of increased uptake would indicate minimal osteoblastic reaction in the periphery (Fig. 4). These bone scintigraphy findings may become a diagnostic pitfall for osteolytic metastasis. Moreover, it is also difficult to reveal intratrabecular metastases and micrometastases on bone scintigraphy, since these metastatic lesions do not cause significant changes of trabecular bone [4].

✉ Seiji Kurata
skur@med.kurume-u.ac.jp

1 Department of Radiology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

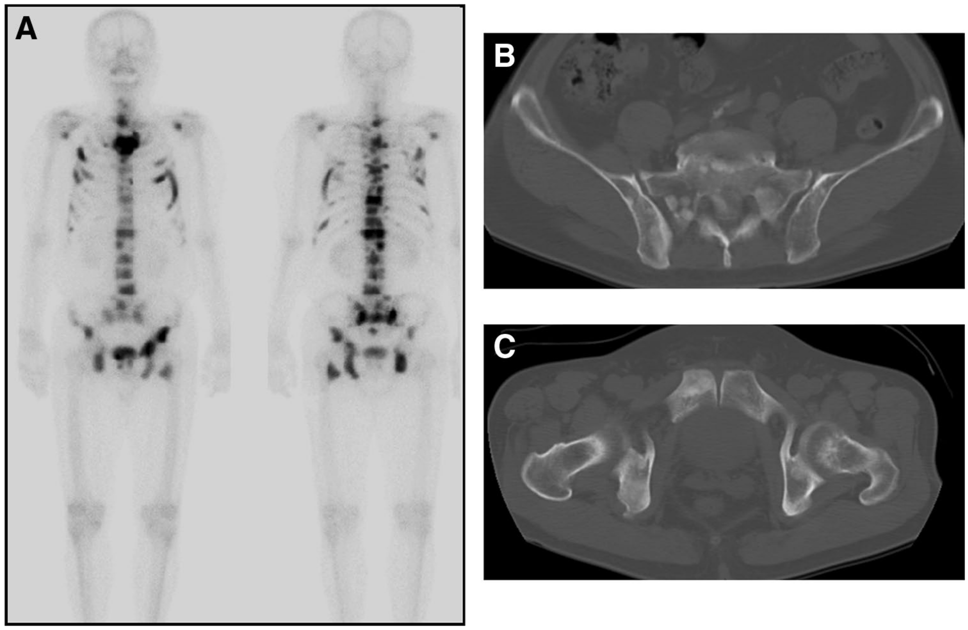

Fig. 1 A 73-year-old man with prostatic carcinoma. **a** Anterior and posterior bone scintigraphy show multiple, randomly distributed foci of abnormal uptake with varying size and intensity. **b**, **c** Axial computed tomography images show multiple osteoblastic changes in the sacrum, right ischium, and pubis

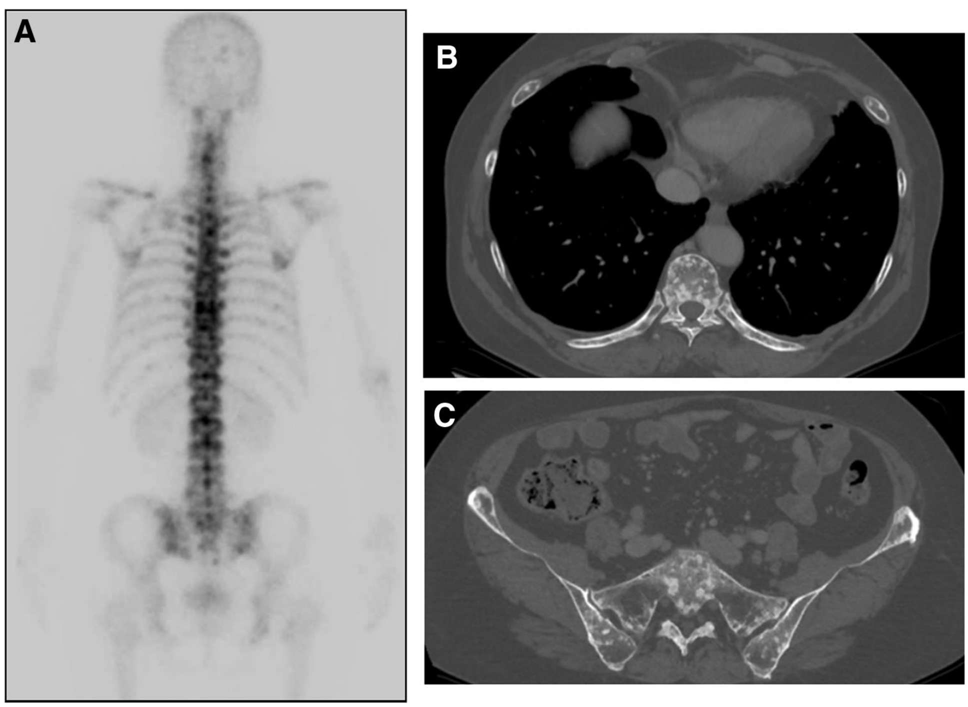

Fig. 2 A 64-year-old woman with ovarian carcinoma. **a** Posterior bone scintigraphy shows multiple slightly increased uptakes in the axial skeleton. **b**, **c** Axial computed tomography images show multiple osteoblastic changes in the axial skeleton

Single photon emission computed tomography (SPECT) complements whole body imaging and may help detect additional bone lesions. It also provides three-dimensional anatomical information that can improve localization of abnormal uptakes [5]. For example, metastasis to the sacrum may be obscured by bladder activity and be missed on planar images. However, SPECT images can clearly reveal focal uptake in the sacrum (Fig. 5).

Metabolic disorders

Metabolic bone disorders are characterized by high bone turnover, which results in increased uptake of bone agents. Excessive parathyroid hormone is common in these conditions and the degree of abnormality on bone scintigraphy is directly related to the severity and duration of the disease [6].

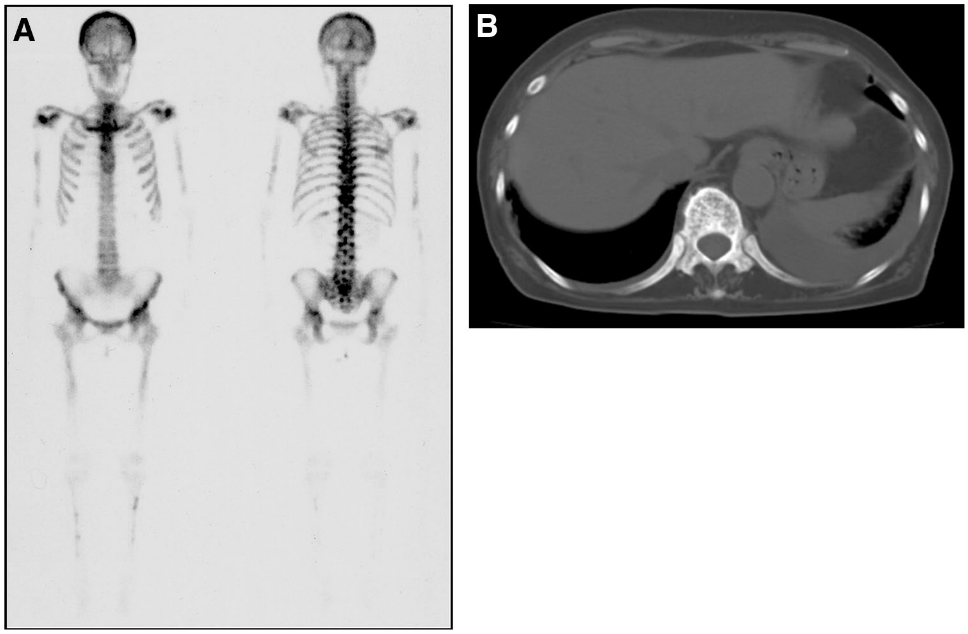

Fig. 3 An 83-year-old woman with gastric carcinoma. **a** Anterior and posterior bone scintigraphy show diffuse, irregularly increased uptake throughout the skeleton. In the scintigram, there is minimal bladder activity without renal activity. This pattern is indicative of diffuse bone metastases and is often referred to as a "super scan". **b** Axial computed tomography image shows diffuse osteoblastic changes in the spine and bilateral ribs

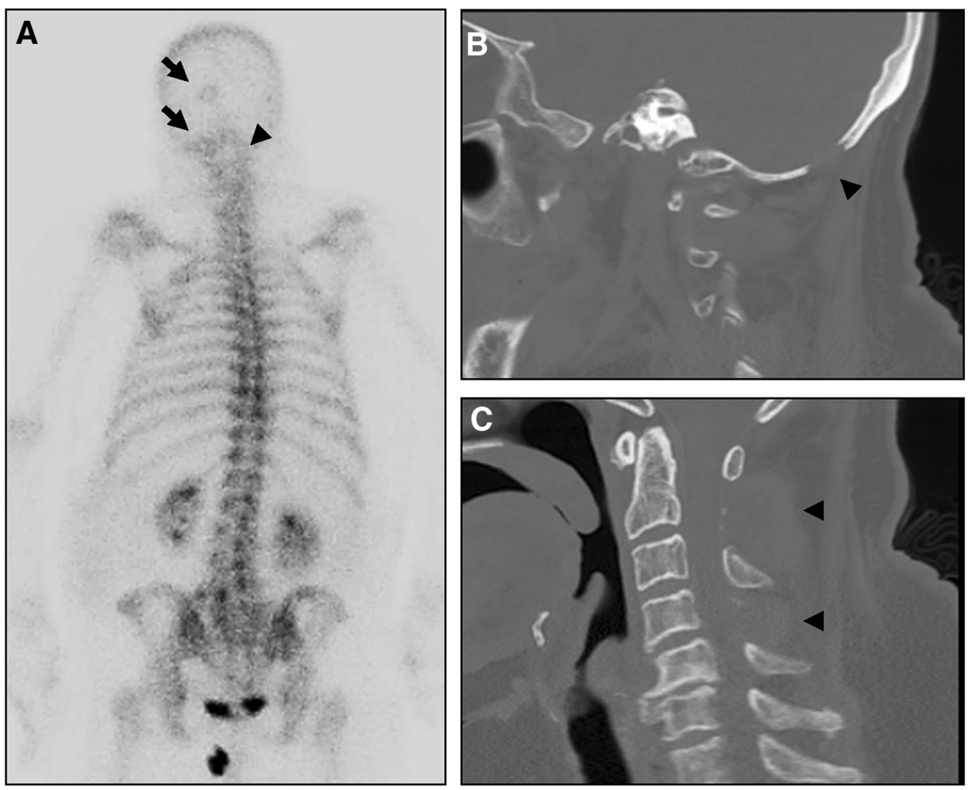

Fig. 4 A 70-year-old man with hepatocellular carcinoma. **a** Posterior bone scintigraphy shows slight rim uptakes (*arrows*) in the skull and absent uptake (*arrowhead*) in the cervical spine. **b**, **c** Sagittal computed tomography images show osteolytic changes in the same regions (*arrowheads*)

Renal osteodystrophy (ROD)

ROD produces changes in bone metabolism due to chronic renal dysfunction. It combines features of secondary hyperparathyroidism, rickets, osteomalacia, and osteoporosis in varying degree. Bone scintigraphy has been acknowledged to be a sensitive method for early detection and assessment of ROD [7]. In patients with high-turnover ROD, uptake throughout the skeleton is markedly increased, especially in the calvaria, and the kidneys frequently appear faint [8] (Fig. 6).

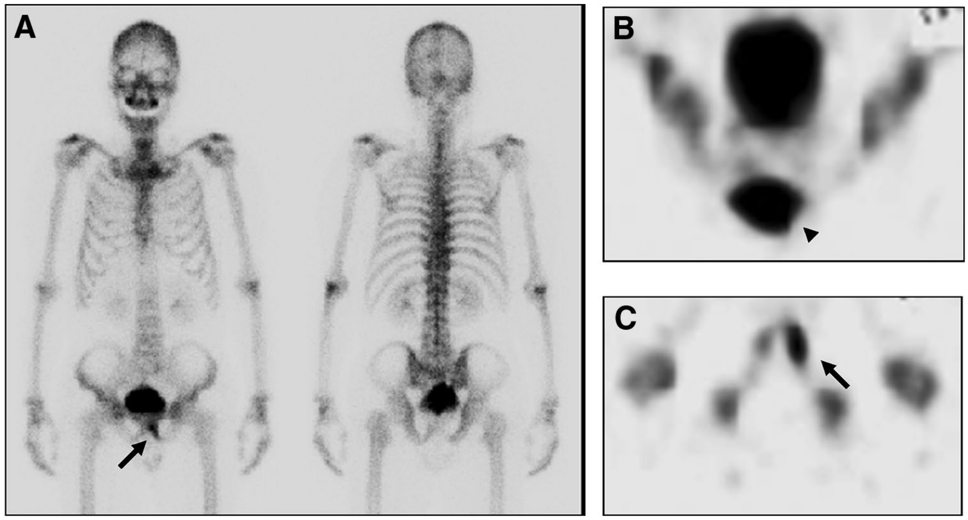

Fig. 5 A 69-year-old man with prostatic carcinoma. **a** Anterior bone scintigraphy shows focal uptake in the left pubis (*arrow*). However, focal uptake in the sacrum is not definite on posterior bone scintigraphy. **b**, **c** Transaxial single-photon emission computed tomography (SPECT) images clearly show focal increased uptakes in the sacrum (*arrowhead*) and left pubis (*arrow*)

Fig. 6 An 83-year-old woman with secondary hyperparathyroidism and a past history of multiple fractures due to trauma. Anterior and posterior bone scintigraphy shows symmetrical generalized uptake throughout the skeleton. These images show the super scan pattern associated with metabolic bone disease. Furthermore, these images show multiple focal uptakes (*arrows*) in the bilateral ribs and right femoral neck due to trauma

Osteomalacia

Osteomalacia results from vitamin D deficiency, which produces profound mineralization defects. In severe cases, there is massive excess of osteoid and markedly reduced mineralization. On bone scintigraphy, abnormal increased uptake is most visible at the periarticular zones and costochondral junctions (Fig. 7a). The reason for increased uptake in osteomalacia is not well known, even if there is an underlying defect in mineralization [8]. Notably, pseudofractures are often detected in osteomalacia (Fig. 7b). Bone scintigraphy is a sensitive tool for identifying pseudofractures, whereas conventional radiology cannot detect these lesions. Furthermore, bone scintigraphy can be used to monitor response to treatment of these metabolic disorders (Fig. 7c).

Primary hyperparathyroidism

Primary hyperparathyroidism is a common disorder that involves increased secretion of parathyroid hormone, leading to hypophosphatemia and hypercalcemia. Bone scintigraphy may show uptakes that range in appearance from normal to that mimicking ROD. The presence of focal increased uptake in primary hyperparathyroidism is uncommon, but may be seen when brown tumors are present (Fig. 8). A brown tumor is characterized by high osteoclastic activity and bone resorption, and is most commonly found in the pelvis, ribs, skull, and jaw. Brown tumors may be misdiagnosed as malignant; therefore, giant cell tumor, fibrous dysplasia, aneurysmal bone cyst, and bone metastasis must be considered in its differential diagnoses [9].

Growth disorder

Fibrous dysplasia (FD)

FD is a benign skeletal developmental disorder of unknown etiology and is characterized by fibrous osseous

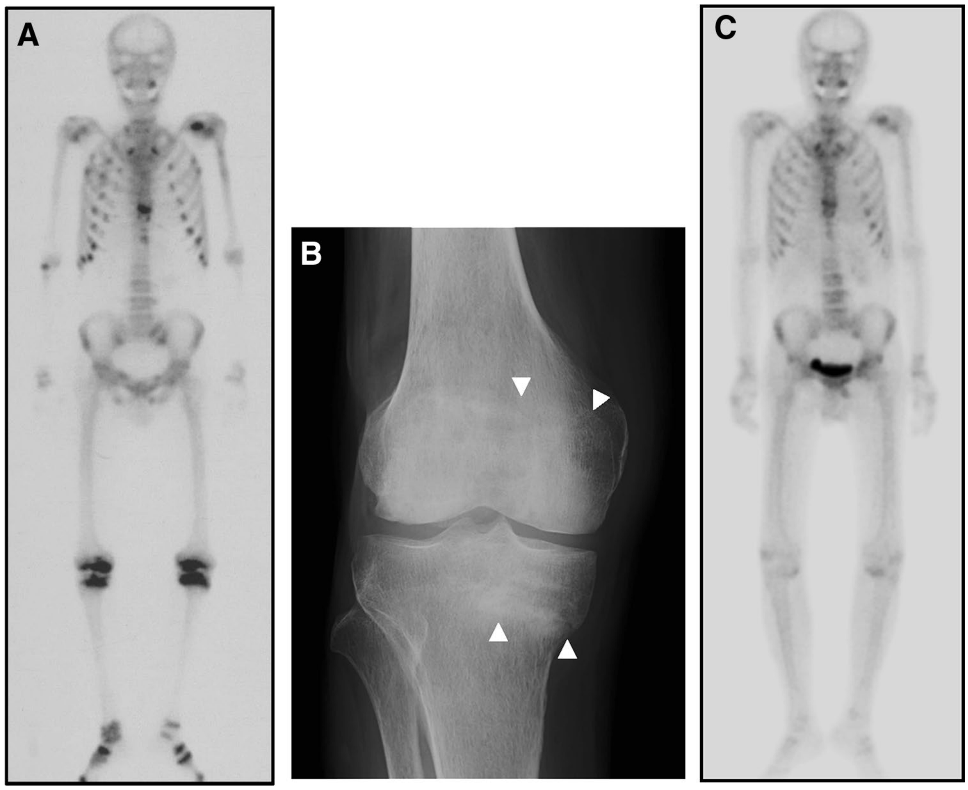

Fig. 7 A 61-year-old man with osteomalacia. **a** Anterior bone scintigraphy shows multiple uptakes in the ribs, costochondral junctions, sternum, pubis, and bilateral knees, ankles, and feet. **b** Anteroposterior radiograph of the right knee shows ill-defined osteolytic lesions with sclerotic changes in the right distal femur and proximal tibia (*arrowheads*). **c** Anterior bone scintigraphy is shown after vitamin D therapy. The patient responds well to vitamin D therapy

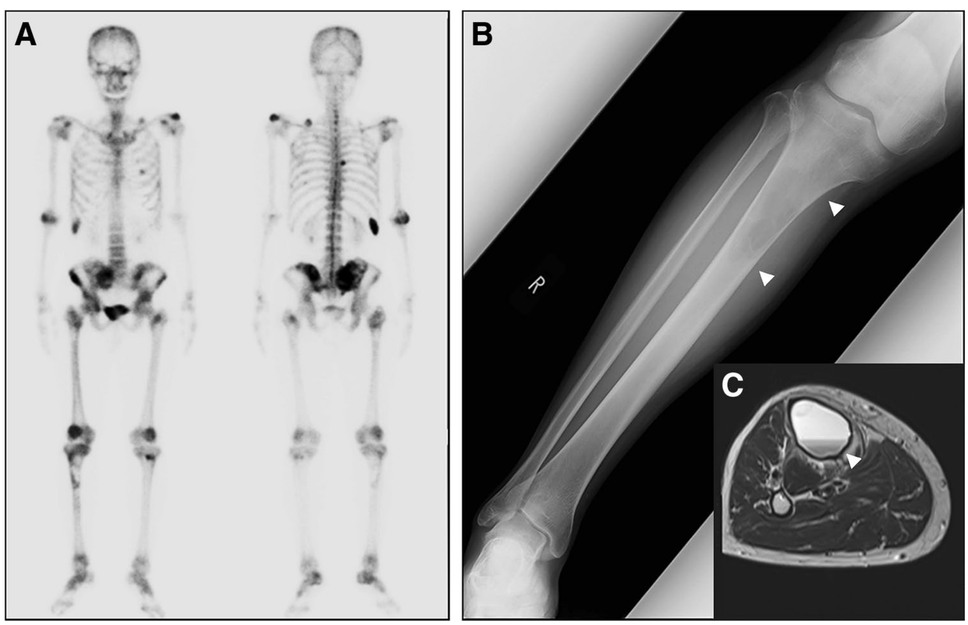

Fig. 8 A 50-year-old man with brown tumors due to primary hyperparathyroidism. **a** Anterior and posterior bone scintigraphy shows multiple uptakes in the bilateral proximal femoral bones, proximal tibia, and ribs, as well as in the pelvis, right humerus, and right scapula. **b** Anteroposterior radiograph of the right lower limb shows multiple, well-defined osteolytic lesions in the right proximal tibia (*arrowheads*). **c** Axial T2-weighted magnetic resonance image shows cystic mass with hemorrhage and fluid–fluid level in the right proximal tibia (*arrowhead*)

metaplasia of the medullary bone [10]. It is most commonly of the monostotic type. On the other hand, polyostotic FD is asymmetrical and tends to be symptomatic earlier, with fractures and deformities in early childhood. Polyostotic FD that is associated with one or more extraskeletal conditions, such as café-au-lait skin pigmentation, sexual precocity, and other endocrinopathies, is known as McCune–Albright syndrome (Fig. 9). Bone scintigraphy demonstrates increased uptake in the involved sites. Search for such polyostotic involvement, which is often asymptomatic, is the main indication for bone scintigraphy [11].

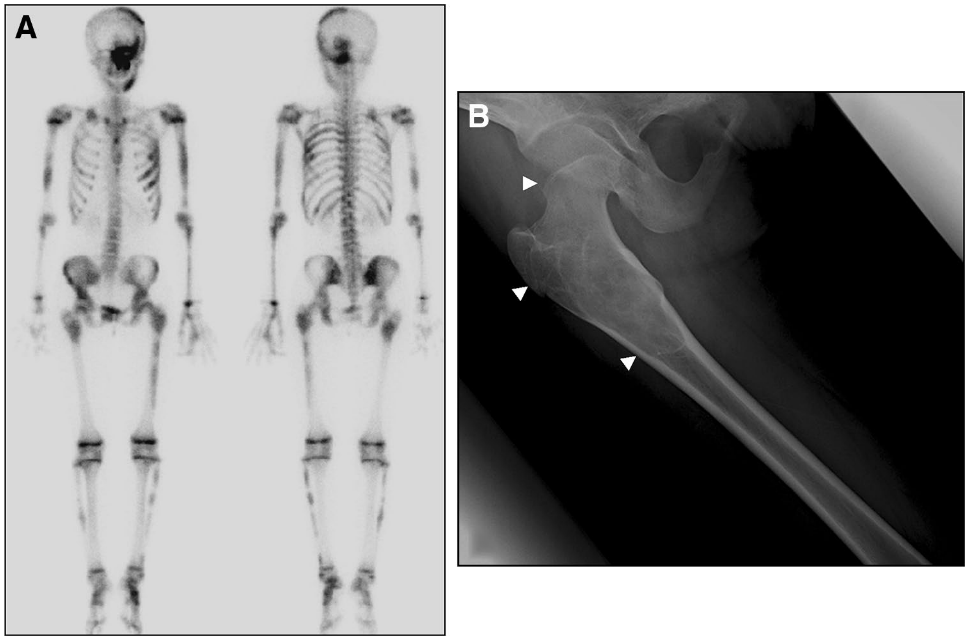

Fig. 9 Polyostotic fibrous dysplasia in a 12-year-old girl with McCune–Albright syndrome. **a** Anterior and posterior bone scintigraphy images show multiple increased uptakes in the axial and appendicular skeleton. **b** Anteroposterior radiograph of the right hip shows a large ground-glass appearance of the right femoral metaphysis and diaphysis with sclerotic margin (*arrowheads*)

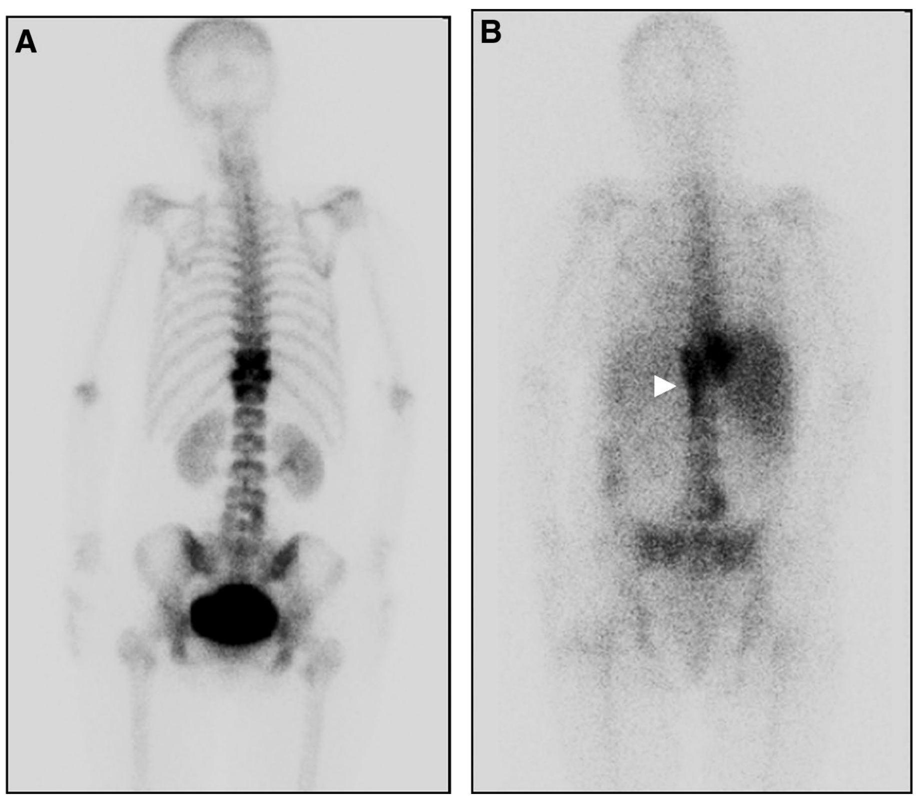

Fig. 10 A 48-year-old woman with osteomyelitis. **a** Posterior bone scintigraphy shows increased uptake in the thoracic spine. **b** Posterior gallium citrate 67 (^{67}Ga) scintigraphy shows increased uptake in the same lesions with extension to the adjacent regions (*arrowhead*)

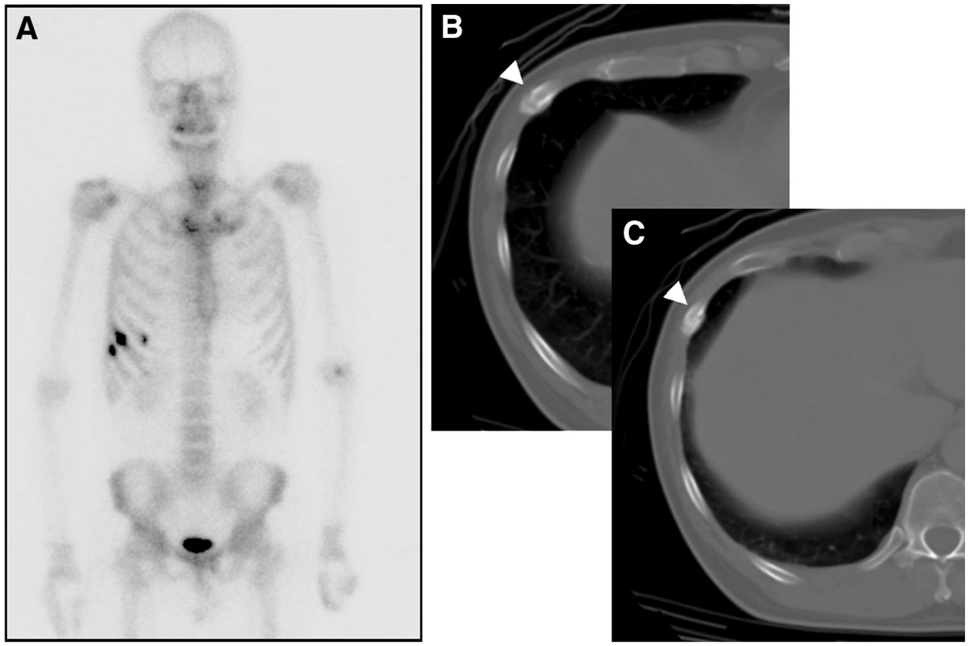

Fig. 11 A 50-year-old man after resection of testicular tumor and without a definite history of trauma. **a** Anterior bone scintigraphy shows multiple increased uptakes in the right-sided ribs. **b**, **c** Axial computed tomography scans show fracture lines in the same locations (*arrowheads*)

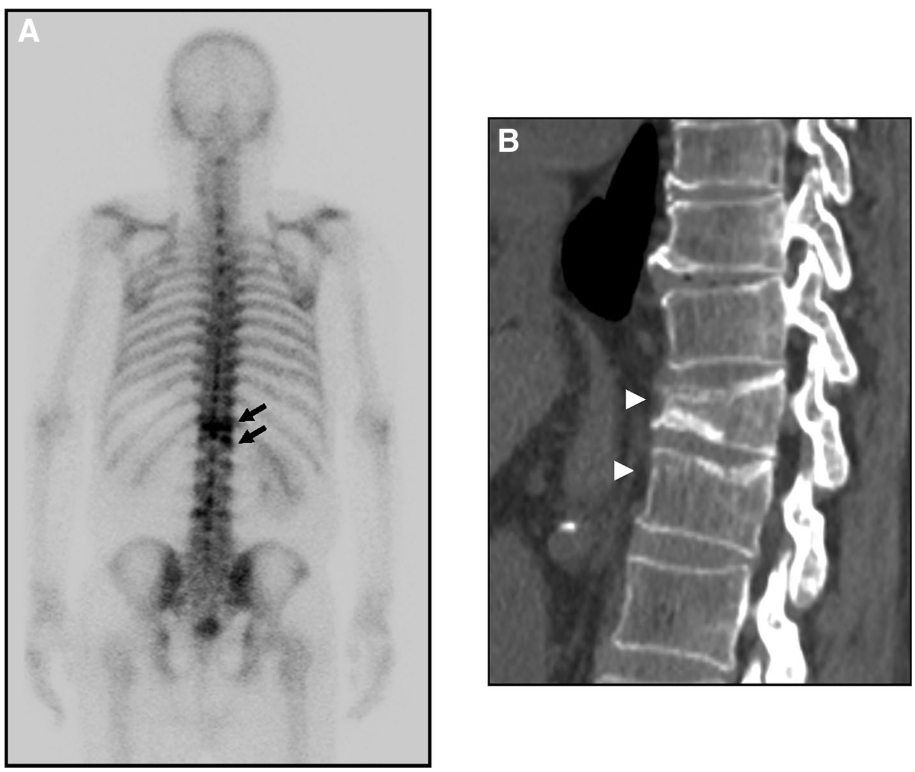

Fig. 12 A 67-year-old man with renal cell carcinoma. **a** Posterior bone scintigraphy shows increased horizontal linear uptakes in the twelfth thoracic vertebra and the first lumber vertebra (*arrows*). **b** Sagittal computed tomography scan shows endplate fractures with deformity in the same locations (*arrowheads*)

Inflammation

Osteomyelitis

Osteomyelitis causes rapid osteoblastic response, which can be readily detected as inflammatory changes on bone scintigraphy (Fig. 10a). Changes can be expected to occur rapidly in the course of any bone and joint infection and bone scintigraphy is of paramount importance to help in early diagnosis. However, conditions associated with increased bone metabolism (e.g., tumors and trauma) may mimic osteomyelitis [12].

Because of diminished specificity of bone scintigraphy, complementary imaging with gallium citrate 67 (^{67}Ga) scintigraphy is often performed [13] (Fig. 10b). ^{67}Ga was reported to have faster uptake and to be more sensitive in detecting osteomyelitis than ^{99m}Tc-labeled diphosphonate. However, because of greater cost and radiation burden, ^{67}Ga may be reserved for patients in whom there is a high clinical suspicion of osteomyelitis that cannot be clearly defined by bone scintigraphy.

Trauma

Changes from traumatic bone injury generally manifest as discrete focal uptakes of similar intensity [14]. Multifocal rib trauma has a characteristic linear or curved distribution of uptake (Fig. 11a). Metastasis to the rib tends to be elongated; on the other hand, a rib fracture tends to be round in shape (Fig. 11b, c).

Furthermore, in older patients, compression fractures and degenerative changes may manifest as areas of increased uptakes on bone scintigraphy. It has a useful role in evaluation of oncologic patients with back pain. Osteoporosis with advancing age has a high risk of fracture due to trauma. If a benign compression fracture is present, the classical bone scintigraphy finding of the fracture is a horizontal linear uptake at the fracture site [15] (Fig. 12a). The differentiation of benign compression fracture from bone metastasis is also important. However, interpreting increased abnormal uptake in the spine could be difficult, since a benign compression fracture or degenerative change may be indistinguishable from bone metastasis. Therefore, plain radiography, computed tomography, or magnetic resonance imaging are often required for additional findings (Fig. 12b).

Conclusions

We have shown the different multiple abnormal uptakes on bone scintigraphy for metastatic bone tumor, metabolic bone disease, trauma, and bone inflammation. We have described the possibilities and limitations of using the pattern of distribution of abnormal uptakes in the differential diagnoses of metastatic bone tumors. We have also shown findings that can be diagnostic pitfalls on bone scintigraphy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Brenner AI, Koshy J, Morey J, Lin C, DiPoce J. The bone scan. Semin Nucl Med. 2012;42:11–26.
2. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004;15:1655–64.
3. Love C, Din AS, Tomas MB, Kalapparambath TP, Palestro CJ. Radionuclide bone imaging: an illustrative review. Radiographics. 2003;23:341–58.
4. Yamaguchi T, Tamai K, Yamato M, Honma K, Ueda Y, Saotome K. Intertrabecular pattern of tumors metastatic to bone. Cancer. 1996;78:1388–94.
5. Murray IP, Dixon J. The role of single photon emission computed tomography in bone scintigraphy. Skelet Radiol. 1989;18:493–505.
6. Ryan PJ, Fogelman I. Bone scintigraphy in metabolic bone disease. Semin Nucl Med. 1997;27:291–305.
7. Fogelman I, Collier BD, Brown ML. Bone scintigraphy: part 3. Bone scanning in metabolic bone disease. J Nucl Med. 1993;34:2247–52.
8. Cook GJ, Gnanasegaran G, Chua S. Miscellaneous indications in bone scintigraphy: metabolic bone diseases and malignant bone tumors. Semin Nucl Med. 2010;40:52–61.
9. Meydan N, Barutca S, Guney E, Boylu S, Savk O, Culhaci N, et al. Brown tumors mimicking bone metastases. J Natl Med Assoc. 2006;98:950–3.
10. Collins MT, Riminucci M, Banco P. Fibrous dysplasia. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 7th ed. Washington, D.C.: American Society for Bone and Mineral Research; 2008. p. 423–7.
11. Bousson V, Rey-Jouvin C, Laredo JD, Le Merrer M, Martin-Duverneuil N, Feydy A, et al. Fibrous dysplasia and McCune-Albright syndrome: imaging for positive and differential diagnoses, prognosis, and follow-up guidelines. Eur J Radiol. 2014;83:1828–42.
12. Brown ML, Collier BD Jr, Fogelman I. Bone scintigraphy: part 1. Oncology and infection. J Nucl Med. 1993;34:2236–40.
13. Love C, Palestro CJ. Radionuclide imaging of inflammation and infection in the acute care setting. Semin Nucl Med. 2013;43:102–13.
14. Collier BD Jr, Fogelman I, Brown ML. Bone scintigraphy: part 2. Orthopedic bone scanning. J Nucl Med. 1993;34:2241–6.
15. Van der Wall H, Murray IPC. Bone scintigraphy in trauma. In: Ell PJ, Gambhir SS, editors. Nuclear medicine in clinical diagnosis and treatment. 3rd ed. London: Churchill Livingstone; 2005. p. 709–20.