



SPECT-CT for characterization of extraosseous uptake of ^{99m}Tc -methylene diphosphonate on bone scintigraphy

Ramya Soundararajan, Niraj Naswa, Punit Sharma, Sellam Karunanithi, Aftab Hasan Nazar, Kalpa Jyoti Das, Chandrasekhar Bal, Arun Malhotra, Rakesh Kumar

ABSTRACT

Bone scintigraphy is a sensitive and popular method for imaging a wide array of benign or malignant skeletal abnormalities. However, the uptake of tracers used for bone scintigraphy may be observed in various extraosseous sites, thereby limiting its specificity. It is difficult to correctly localize such sites of uptake on planar bone scintigraphy alone. The addition of hybrid single-photon emission computed tomography-computed tomography (SPECT-CT) under such circumstances is very useful. The present essay illustrates the commonly encountered extraosseous uptake of ^{99m}Tc -methylene diphosphonate (MDP) and the usefulness of hybrid SPECT-CT in clarifying ^{99m}Tc -MDP uptake.

The ability to assess new bone formation makes bone scintigraphy a popular noninvasive diagnostic technique for imaging the skeletal system. Pathologic entities that commonly demonstrate increased uptake on bone scintigraphy are primary bone tumors, skeletal metastases, infections, and sites of skeletal trauma. Bone-seeking tracers such as ^{99m}Tc -methylene diphosphonate (MDP) and its analogs localize to bone by chemisorption to the surface of hydroxyapatite crystals (1). Sites of new bone formation show increased uptake because of high regional perfusion and increased areas of proliferation. On occasion, certain abnormal processes involving soft tissues can also cause skeletal accumulation of radiotracer (extraosseous uptake) on bone scintigraphy apart from the physiologic excretion of tracer through the urinary tract (2). Probable mechanisms that have been proposed to explain extraosseous uptake of ^{99m}Tc -MDP include a) increased regional vascularity and permeability; b) tumor necrosis with or without calcification; c) metastatic calcification in renal failure; d) increased tissue calcium concentration; e) serum hypocalcemia of any etiology; f) presence of collagen; and g) improper labeling of the radionuclide (3, 4). Knowledge regarding these potentially confusing entities is important because they may hinder correct interpretation of the disease in question. Identification of such nonosseous uptake becomes particularly difficult if planar scintigraphy is used alone. Additional use of hybrid single-photon emission computed tomography (SPECT)-computed tomography (CT) helps in proper anatomical localization of abnormal uptake noted on bone scintigraphy and improves the quality of interpretation. SPECT-CT increases the sensitivity of bone scintigraphy by detecting additional lesions, and the exclusion of sites of physiological tracer uptake also increases specificity. Attenuation and photon scatter correction of nuclear medicine images by hybrid imaging helps us to obtain more accurate image data. The functional significance of indeterminate bone lesions detected on anatomical imaging studies can also be characterized by SPECT-CT. This pictorial essay reviews a few examples of abnormal processes that may cause extraosseous uptake on bone scintigraphy encountered at our institute and highlights the significance of proper anatomical localization using SPECT-CT.

From the Department of Nuclear Medicine (R.K. ✉ rkphulia@hotmail.com), All India Institute of Medical Sciences, New Delhi, India.

Received 12 February 2013; revision requested 3 March 2013; revision received 6 March 2013; accepted 13 March 2013.

Published online 3 June 2013.
DOI 10.5152/dir.2013.054

Extraosseous uptake in neoplastic diseases

Metastatic disease

Metastatic diseases such as malignant pleural and pericardial effusion, hepatic metastases, and calcific metastases of osteosarcoma accumulate

^{99m}Tc -MDP (2). Cellular necrosis due to ischemia or fat necrosis due to enzymatic action leads to deposition of calcium. Under normocalcemic conditions, deposition of calcium occurs in necrotic tissue and is called dystrophic calcification (5). Tissue damage at times leads to collagen degeneration and is associated with calcium deposition. This mechanism operates when locoregional lymph nodes involved in the primary neoplastic disease becomes enlarged and accumulate calcium after necrosis. Fig. 1 shows such a case in a patient with prostate carcinoma who was referred for metastatic work-up. SPECT-CT images showed ^{99m}Tc -MDP accumulation in the enlarged left inguinal lymph node along with other metastatic sites. In the above case, SPECT-CT helped us to delineate the lymph node that, on planar imaging, was thought to be one of the metastatic skeletal deposits.

The liver is a common and frequent extraosseous site for metastatic deposits that sometimes also accumulate ^{99m}Tc -MDP. Because the liver is extensively vascular and its high blood flow and dual blood supply make it the most frequent site of metastases, metastatic deposits are observed as focal areas of increased activity in the right lower hemithorax, usually due to carcinoma of the breast and lung, and adenocarcinoma of the gastrointestinal tract. The accumulation of ^{99m}Tc -MDP is favored by regional blood flow variations, necrosis, and calcification in liver metastasis (6, 7) (Fig. 2).

Certain metastatic tissues are metabolically similar to bone and also have the property of concentrating ^{99m}Tc -MDP. The osteoid matrix produced by metastases from osteogenic sarcoma is one of the mechanisms by which extraosseous metastases from osteosarcomas concentrate ^{99m}Tc -MDP (8). Fig. 3 shows an extraosseous metastatic deposit in the vastus lateralis muscle in the right thigh in an operated osteosarcoma of the right distal femur. SPECT-CT improved the clinical significance of this case by revealing extraosseous metastasis that was initially thought

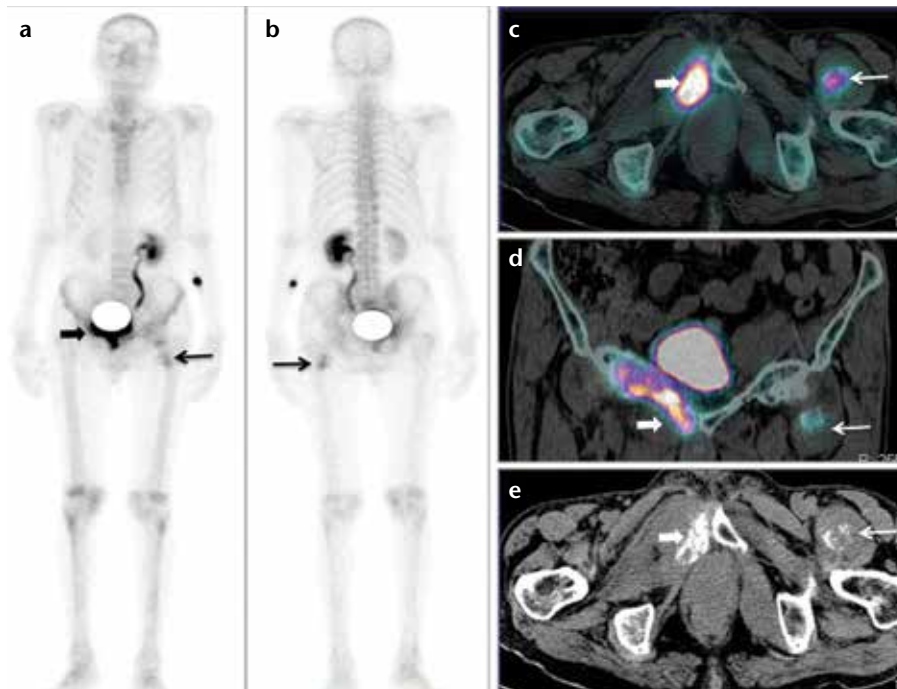


Figure 1. a–e. A 66-year-old man, a known case of prostate carcinoma who underwent metastatic work-up. His prostate-specific antigen level was 56 ng/mL. The anterior ^{99m}Tc -MDP planar scintigraphy image (a) shows focally increased radiotracer uptake in the right superior pubic ramus and symphysis pubis (*thick arrow*) and also in the lesser trochanter of the left femur (*thin arrow*). The posterior planar image (b) shows the same (*arrow*). Axial (c) and coronal (d) SPECT-CT images of the pelvis localize the increased radiotracer uptake in the right superior pubic ramus (*thick arrows*) and left inguinal lymph node (*thin arrows*). These changes correspond to a lytic destructive lesion in the right superior pubic ramus (*thick arrow*) and calcification in the enlarged left inguinal lymph node (*thin arrow*) in the unenhanced CT image (e).

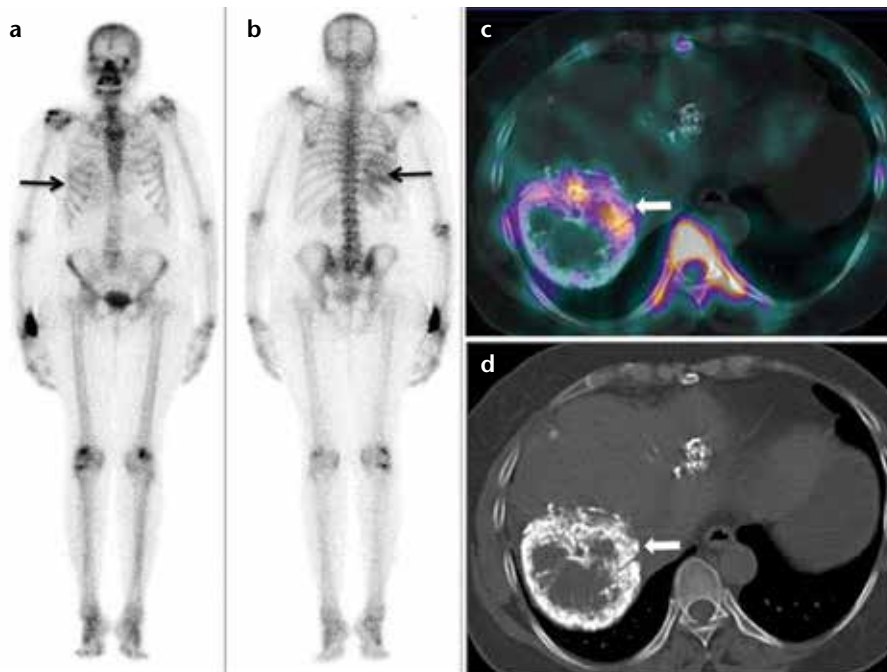


Figure 2. a–d. A 45-year-old woman, a follow-up case of operated breast carcinoma, who was referred for metastatic work-up. Anterior (a) and posterior (b) planar scintigraphy images reveal abnormally increased radiotracer uptake in the right lower hemithorax (*arrows*). The axial section of fused SPECT-CT image of the abdomen (c) incidentally showed a large calcified hypodense lesion in the right lobe of the liver with further diffusely increased radiotracer uptake in the periphery (*arrow*). The axial section of the corresponding unenhanced CT image (d) also depicts a large calcified hypodense lesion in the right lobe of the liver (*arrow*).

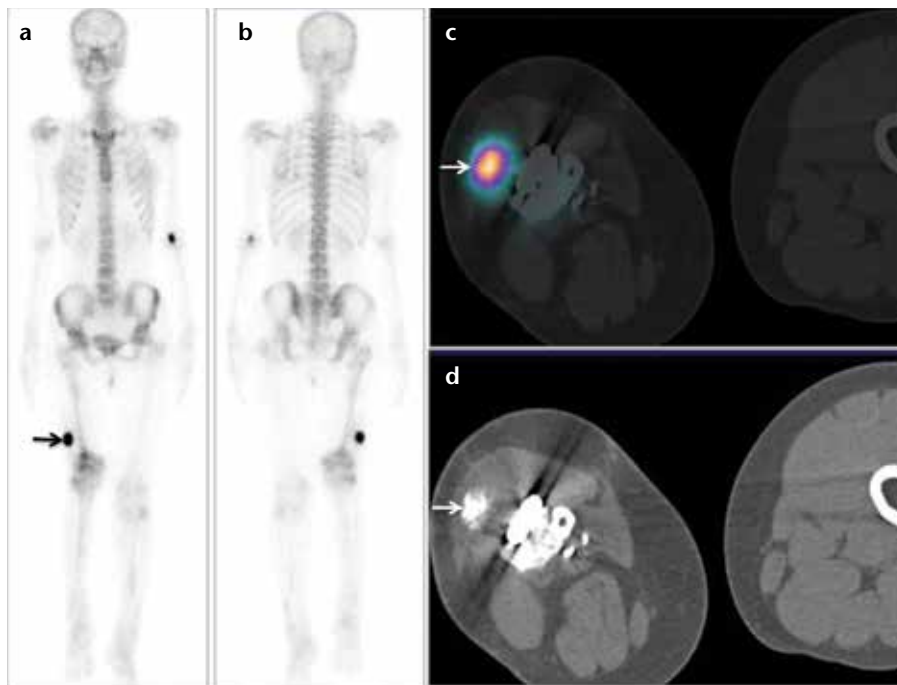


Figure 3. a–d. A 17-year-old girl who was operated for osteosarcoma of the right distal femur one year before and now presented with pain in the right thigh. She was referred for a bone scan for suspected local recurrence at the operated site. Anterior (a) and posterior images (b) of ^{99m}Tc -MDP planar scintigraphy show a focal area of increased radiotracer uptake lateral to the distal shaft of the right femur (arrow). The axial section of fused SPECT-CT image of the right distal thigh (c) localizes a focal area of increased radiotracer uptake (arrow) in the vastus lateralis muscle corresponding to a calcified soft tissue nodule in the vastus lateralis muscle in the right thigh in CT image (d, arrow). On biopsy, the focal area was revealed to be a calcified metastatic deposit in the adjacent muscle, explaining the reason for pain.

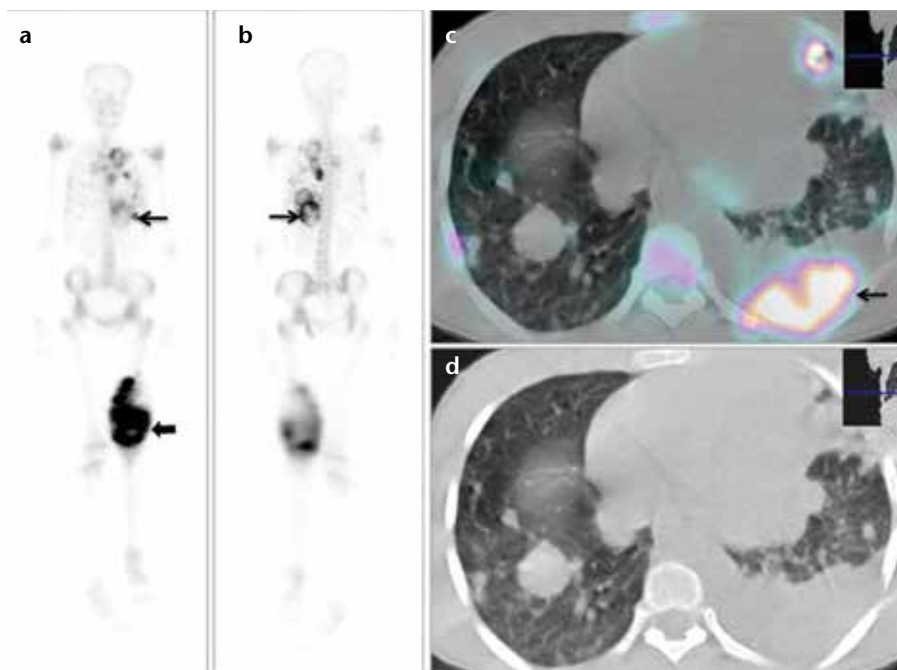


Figure 4. a–d. A 19-year-old girl, a known case of osteosarcoma of the left distal femur was referred for metastatic work-up before surgery. Anterior (a) and posterior (b) planar ^{99m}Tc -MDP scintigraphy images reveal focal areas of abnormal heterogeneously increased radiotracer uptake in the left hemithorax (thin arrows) and large heterogeneously increased radiotracer uptake in the primary tumor in the left distal femur (thick arrow). Axial sections of fused SPECT-CT (c) revealed multiple soft tissue nodular lesions in the bilateral lung parenchyma, with increased radiotracer uptake in the left lung (arrow). CT image of the chest (d) also shows the same. These findings were consistent with osteogenic lung metastasis.

to be external contamination on planar bone scintigraphy. Additionally, Fig. 4 shows extensive ^{99m}Tc -MDP-concentrating osteogenic metastases in the right lung field in another patient with osteosarcoma.

After intravenous injection, in addition to osseous uptake and renal excretion, ^{99m}Tc -MDP rapidly distributes into the extracellular compartment. Malignant pleural effusions and peritoneal ascites occasionally are associated with uptake of ^{99m}Tc -MDP and can be identified on bone scintigraphy by a diffuse increase in radiotracer uptake in the hemithorax, indicating malignant pleural effusion, a dangerous sign in patients screened for skeletal metastases (9). Involvement of the pleural or peritoneal lining by neoplastic cells alters the capillary permeability through direct serosal involvement or lymphatic obstruction. This is increased in malignant effusions, which permit rapid diffusion of the radiopharmaceutical into the effusion, and because the blood concentration of the radiopharmaceutical is high, this diffusion easily occurs (8). Fig. 5 shows a case of breast carcinoma with a diffuse increase in tracer uptake in the left hemithorax due to malignant pleural effusion. Although suspected on planar images, it was confirmed with SPECT-CT.

Primary tumors

Primary neoplasms, both benign and malignant, such as carcinomas of the breast and colon, as well as neuroblastoma and lymphoma, sometimes accumulate ^{99m}Tc -MDP (2). In a normal postpubertal population, nonspecific symmetric uptake occurs in both breasts (10). Uptake of ^{99m}Tc -MDP in primary breast carcinoma is also common. Fig. 6 shows a focal area of radiotracer accumulation in the right anterior chest wall on planar images that corresponds to the breast lesion with calcification on SPECT-CT imaging. The exact mechanism of such uptake of radiotracer is still uncertain, and various factors have been proposed. Histological evidence of calcium deposition has been proposed to be the

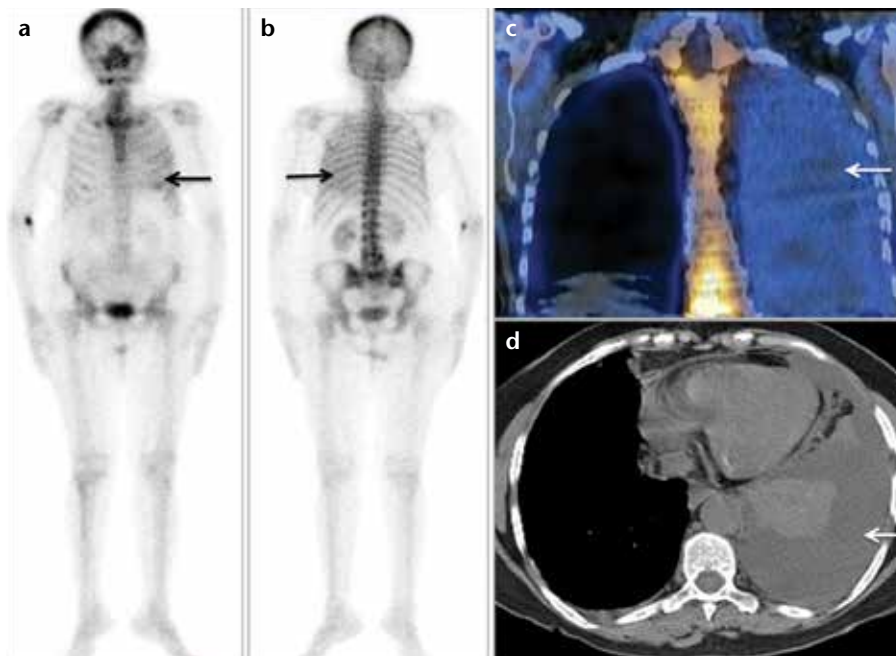


Figure 5. a–d. A 55-year-old woman, a follow-up case of operated right breast carcinoma, presented with a complaint of left-side chest pain and was referred for suspected metastasis. Anterior (a) and posterior (b) planar images of ^{99m}Tc -MDP scintigraphy show diffusely increased radiotracer uptake in the left hemithorax (arrows). Transaxial fused SPECT-CT (c) and CT (d) images depict diffusely increased radiotracer uptake in the pleural effusion noted on the left side (c, arrow) along with evidence of a collapsed left lung, explaining the left chest pain (d, arrow).

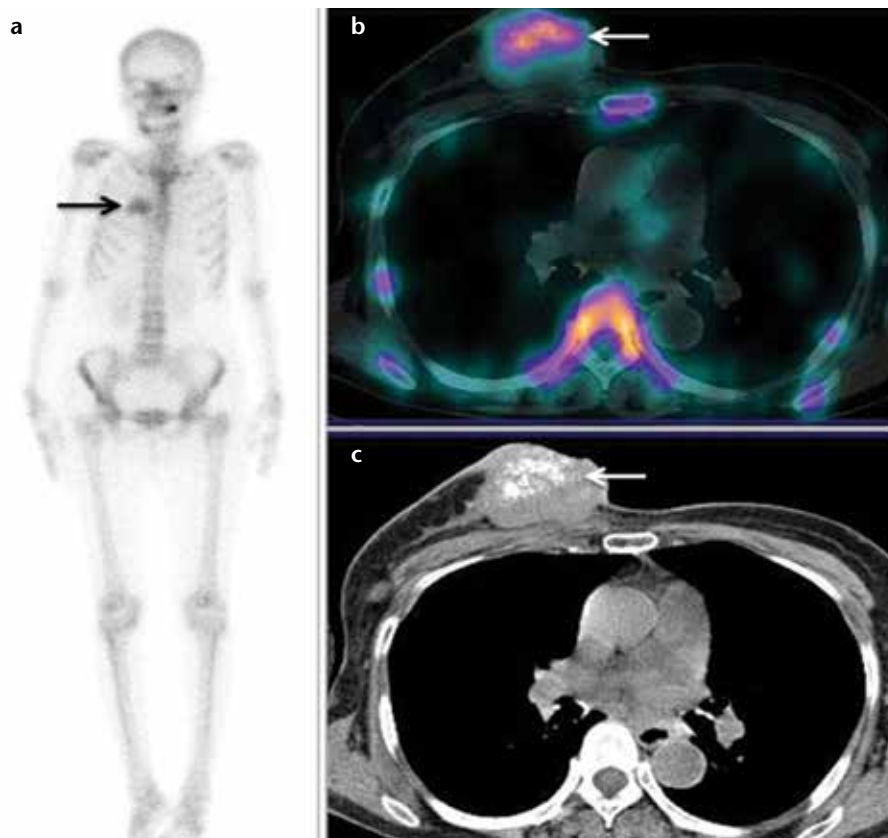


Figure 6. a–c. A 60-year-old woman with proven carcinoma of the right breast, was referred for routine metastatic work-up. The ^{99m}Tc -MDP planar bone scintigraphy anterior planar image (a) shows a focal area of increased radiotracer uptake in the right chest wall (arrow). Because of the suspicion of a metastatic bony lesion, SPECT-CT was performed. Axial SPECT-CT image of the chest (b) localized increased radiotracer uptake in an irregular soft tissue density mass (arrow) in the right breast parenchyma corresponding to coarse calcification in the primary tumor mass, as observed in axial sections of unenhanced CT image of the chest (c, arrow).

most important factor. Increased tumor vascularity is also an important cause of ^{99m}Tc -MDP uptake (11). Adenocarcinomas of the lung, breast, or gastrointestinal tract with a mucinous component possess a glycoprotein that is similar to ossifying cartilage biochemically and binds calcium salts; in turn, this glycoprotein also accumulates ^{99m}Tc -MDP (8).

Extrasosseous uptake due to metabolic causes

Metabolic causes such as serum hypercalcemia of any cause, such as renal failure, hepatocellular disease, sarcoidosis, sickle cell anemia, thalassemia, gout, or amyloidosis (2), if present, concentrates ^{99m}Tc -MDP and provide indirect evidence of the pathology. Serum calcium, phosphorus, and magnesium are within normal limits and are kept regulated under the influence of parathyroid hormone. Disturbances of calcium metabolism, particularly in hyperparathyroidism, lead to metastatic calcification, which refers to calcium deposition in tissues subjected to hypercalcemia. Metastatic calcification may be observed with increased secretion of parathyroid hormone, increased resorption of bone, vitamin D-related disorders, and renal osteodystrophy leading to secondary hyperparathyroidism (5). Alkaline environments in tissues favor calcium and phosphorus deposition in areas of metastatic calcification. Serum hypercalcemia leads to ^{99m}Tc -MDP accumulation in tissues with a high-alkaline environment such as alveolar walls of lungs, tubules of kidneys, and gastric mucosa. Tumor-induced hypercalcemia and metastatic calcification are common. Secretion of systemically or locally active humoral mediators is responsible for the associated bone destruction and consequent severe hypercalcemia (12). Tumor-induced metastatic calcification may involve multiple organs. Fig. 7 shows a case of breast carcinoma presenting with hypercalcemia and diffusely increased radiotracer uptake in bilateral lung fields and the stomach (best appreciated on SPECT-CT images)

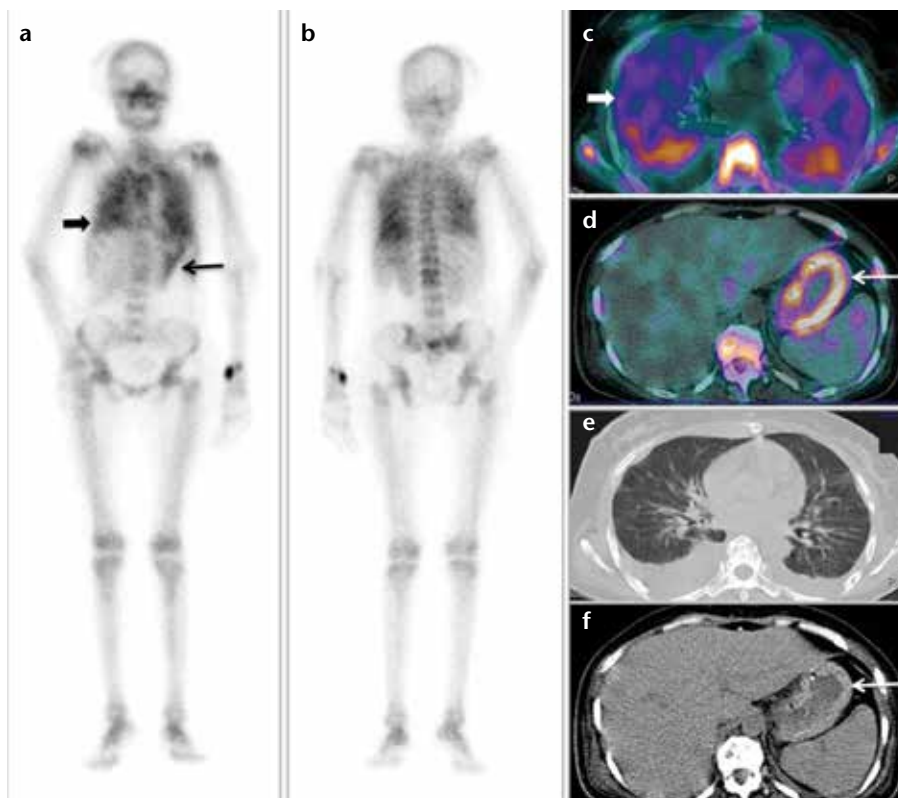


Figure 7. a–f. A 40-year-old woman with known carcinoma of the right breast was referred for metastatic work-up. Increased radiotracer uptake in multiple thoraco-lumbar vertebrae was noted on planar bone scintigraphy. Additionally, anterior (a) and posterior (b) ^{99m}Tc -MDP planar scintigraphy images show diffusely increased radiotracer uptake in both lungs (*thick arrow*, a) and the stomach (*thin arrow*, a). This was confirmed by fused SPECT-CT images (c, d), in which axial sections of the thorax (c) revealed diffusely increased tracer uptake in the bilateral lung fields (*arrow*), and axial sections of the abdomen (d) revealed increased tracer uptake in the stomach wall (*arrow*). Unenhanced axial CT image of the chest (e) shows no obvious lung parenchymal changes, and axial CT image of abdomen (f) shows specks of calcification in the stomach wall (*arrow*). On further investigation, the patient was found to have hypercalcemia (serum calcium level, 16 mg/dL).

in addition to metastases in multiple thoraco-lumbar vertebrae.

Extrasosseous uptake due to genitourinary causes

Physiologic excretion of ^{99m}Tc -MDP occurs through the kidneys and urinary tract. Structural or functional abnormalities of the urinary tract causing tracer accumulation are common. Diseases such as renal or ureteric calculi, hydronephrosis and nephritis accumulate ^{99m}Tc -MDP. The hydronephrosis causes tracer accumulation in the pelvicalyceal system, whereas interstitial diseases cause symmetrical retention of radiotracer in the kidneys. Ectopic or malpositioned kidneys also become an unusual cause of extrasosseous uptake during bone scintigraphy (13). Renal or ureteric calcu-

li comprising calcium oxalate crystals also sometimes causes adsorption of ^{99m}Tc -MDP onto the surface of calcium salts. Ureteric calculi can be observed as a focal area of increased radiotracer uptake, and when it is in the region of the pelvic ureter, it may be confused with skeletal metastases in patients referred for metastatic work up. SPECT-CT is extremely useful in such cases, as shown in Fig. 8.

Extrasosseous uptake due to trauma

Traumatic causes such as myositis ossificans, muscle necrosis, contusion, hematoma, and surgical and intramuscular injection sites show increased uptake of ^{99m}Tc -MDP. Myositis ossificans occurs after trauma due to reactive new bone formation at the traumatic site. The fibroblasts present in the lesion re-

cruit proliferating osteoblasts, leading to the formation of new woven bone that shows avid ^{99m}Tc -MDP uptake. Long-standing, matured lesions show heterotopic ossification in the skeletal muscle on CT but are less avid for ^{99m}Tc -MDP uptake (14). The ^{99m}Tc -MDP uptake also occurs in muscles around joints in cases of paraplegia because of the loss of sensation and unperceived repeated trauma (Fig. 9) (13).

Other causes

Certain other etiologies can concentrate ^{99m}Tc -MDP (3): infections including cellulitis, abscess, synovitis, and pneumonia; vascular conditions including aneurysms, venous thrombosis, lymphatic obstruction, arterial injections, vascular calcification, and myocardial infarction; artifacts including improper preparation of radiopharmaceutical and urine contamination; drugs such as chemotherapeutic agents, vitamin D (hypervitaminosis D), iron dextran, and intravenous contrast after administration of ^{99m}Tc -MDP; and miscellaneous conditions including connective tissue disorders, breast prosthesis, and fibrothorax.

Conclusion

Extrasosseous uptake of ^{99m}Tc -MDP on skeletal scintigraphy is a common finding. We have briefly explained the various possible pathophysiological causes of extrasosseous uptake. Familiarity with and increased awareness of the conditions causing extrasosseous uptake will enhance the quality of interpretation of bone scintigraphy, avoid unnecessary errors in its reporting, and increase its diagnostic value. The use of hybrid SPECT-CT combines the strength of anatomical and functional imaging, both of which help in the proper anatomical localization of focal uptake, and improves the overall diagnostic accuracy of bone scintigraphy. Additionally, exclusion of disease by identification of physiological uptake and accurate identification of anatomical sites of extrasosseous focus increases the specificity of bone scintigraphy, which has a direct impact on patient management.

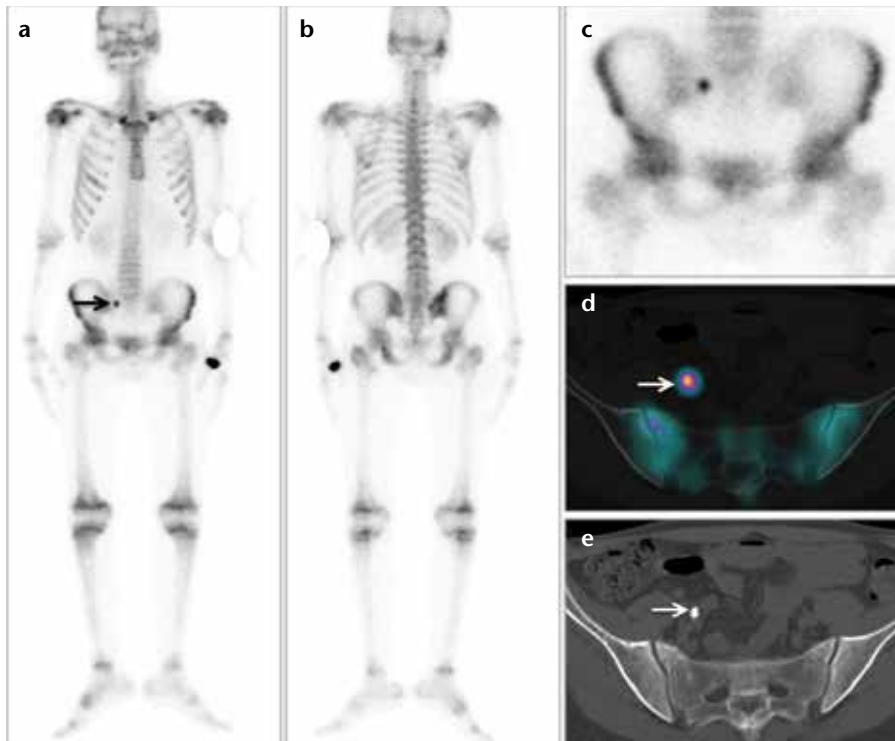


Figure 8. a–e. A 17-year-old boy, a known case of acute lymphoid leukemia was referred for screening for any bony involvement. Anterior (a) and posterior (b) planar images of ^{99m}Tc -MDP planar scintigraphy reveal a focal area of increased radiotracer uptake in the region of the right sacroiliac joint (a, arrow) that is better appreciated in the zoomed image (c). Axial fused SPECT-CT image of the pelvic region (d) shows increased radiotracer uptake in the right ureteric calculi (arrow) that is also observed in unenhanced CT image (e, arrow).

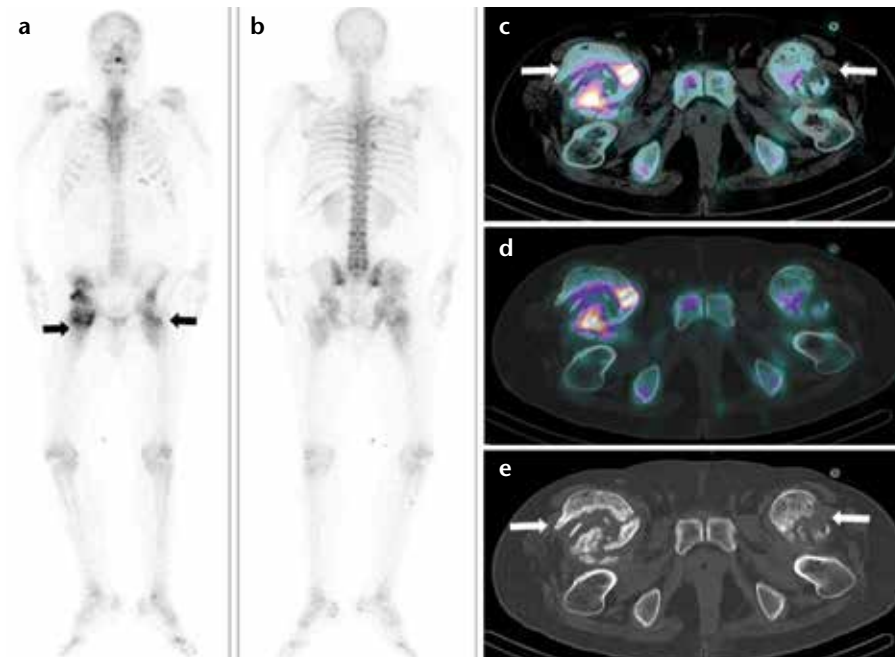


Figure 9. a–e. A 32-year-old man presented with traumatic paraplegia since one year and gradually developed hard swelling around the right hip joint. He was referred to rule out suspected heterotopic ossification around the hip joint and, if the condition was present, to look for its maturity. Anterior (a) and posterior (b) images on ^{99m}Tc -MDP planar scintigraphy show diffusely increased radiotracer uptake around the right and left hip joints (arrows). Axial fused SPECT-CT image of the hips shows increased radiotracer uptake, with dense calcification in the anterior compartmental muscles in the right and left thigh in the soft tissue window (c, arrows) and also in the bone window (d), as well as in unenhanced CT image (e, arrows).

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

- Galasko CS. Mechanism of uptake of bone imaging isotopes by skeletal metastases. *Clin Nucl Med* 1980; 5:565–568. [CrossRef]
- Loutfi I, Collier BD, Mohammed AM. Nonosseous abnormalities on bone scans. *J Nucl Med Technol* 2003; 31:149–153.
- Wilbur MJ, Gagliardi JA, Riccio GJ, et al. Soft tissue uptake in radionuclide musculoskeletal imaging. *Applied Radiology* 1997; 26:30–37. [CrossRef]
- Vallabhajosula S, Owunwanne A. Pathophysiology and mechanisms of radiopharmaceutical localization. In: Elgazzar A, ed. *The pathophysiologic basis of nuclear medicine*. 2nd ed. Berlin-Heidelberg: Springer-Verlag, 2006; 179. [CrossRef]
- Kumar V, Abbas AK, Aster JC, Fausto N. Cellular responses to stress and toxic results. In: Kumar V, Abbas AK, Aster JC, Fausto N, eds. *Robbins and Cotran pathologic basis of disease*. 8th ed. Philadelphia: WB Saunders, 2010; 20–21.
- Romyn AM, Bushnell DL, Freeman ML, Kaplan E. Visualization of metastatic liver disease on technetium-99m bone scintigraphy. *Clin Nucl Med* 1987; 12:264–267. [CrossRef]
- Senda M, Tamak N, Torizuka K, et al. Accumulation of Tc-99m methylene diphosphonate in calcified metastatic lesions of the liver from colonic carcinoma. *Clin Nucl Med* 1985; 10:9–12. [CrossRef]
- Zuckier LS, Freeman LM. Nonosseous, nonurologic uptake on bone scintigraphy: atlas and analysis. *Semin Nucl Med* 2010; 40:242–256. [CrossRef]
- Siegel ME, Walker WJ, Campbell JL. Accumulation of Tc-99m-diphosphonate in malignant pleural effusions: detection and verification. *J Nucl Med* 1975; 16:883–885.
- Mcdougall IR, Pistenma DA. Concentration of ^{99m}Tc diphosphonate in breast tissue. *Radiology* 1974; 112:655–657.
- Silberstein EB. Nonosseous localization of bone seeking pharmaceuticals. In: Silberstein EB, ed. *Bone scintigraphy*. Mount Kisco: Futura, 1985; 347–370.
- Alarcon-Segovia D, Lazo C, Sepulveda J, et al. Uptake of Tc-99m-labeled phosphates by gouty tophi. *J Rheumatol* 1974; 1:314–318.
- Peller PJ, Ho VB, Kransdorf MJ. Extrasosseous Tc-99m MDP uptake: a pathophysiologic approach. *Radiographics* 1993; 13:715–734.
- Orzel JA, Rudd TG. Heterotopic bone formation: clinical, laboratory, and imaging correlation. *J Nucl Med* 1985; 26:125–132.