



Altered Biodistribution of Radiopharmaceuticals Used in Bone Scintigraphy

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Bone scintigraphy has remained a mainstay of clinical nuclear medicine for more than 4 decades. Extensive medical literature has developed surrounding the etiology and significance of alterations in distribution of bone radiopharmaceuticals. Altered biodistribution may be of a global nature, reflecting altered partition of radiopharmaceutical between bone and soft tissues, or more focal, reflecting regional abnormalities, including those related to bone or soft tissues. A third category of alterations in the distribution of bone radiopharmaceuticals is those due to errors and blunders, colloquially termed “artifactual” in the medical imaging literature. Being cognizant of these unexpected abnormalities, and understanding their etiology, will prepare the reader to more readily appreciate the significance of these findings when encountered in clinical practice. *Semin Nucl Med* 45:81-96 © 2015 Elsevier Inc. All rights reserved.

Introduction

Bone scintigraphy has remained a mainstay of clinical nuclear medicine for more than 4 decades¹ and is typically performed to assess 1 or more focal abnormalities of bone including metastases, osteomyelitis, and a host of other degenerative, inflammatory, and orthopedic disorders. Generally, ^{99m}Tc-labeled phosphonates are employed for routine planar or tomographic single-photon imaging of the skeleton.² The commonly used radiopharmaceutical ^{99m}Tc-methylene diphosphonate (MDP) represents this group in our discussion. Although ¹⁸F-NaF positron emission tomographic imaging is being performed more frequently to assess bony abnormalities,^{3,4} routine clinical experience with this agent, especially with respect to artifacts, is much more limited than that of MDP.

Delayed phase bone scintigraphy is typically performed at 2-5 hours after intravenous injection of a radiopharmaceutical.⁵ As a general rule, at this point, skeletal uptake is relatively uniform and soft tissue activity is negligible, with the exception of a variable amount of radiopharmaceutical retained in the renal parenchyma, collecting system, and urinary bladder. Unanticipated deviations from this normal distribution may occur on occasion and are the subject of this review. In some

cases, a global variation in bone uptake is encountered, whereas in others, the alteration in distribution of bone-seeking radiopharmaceuticals is regional. Abnormalities may affect bone, generalized soft tissues, and visceral organs.

By categorizing these unanticipated abnormalities and their etiology, the reader will more readily appreciate similar findings and their significance when subsequently encountered. In some instances, these anomalies may reflect serious underlying diseases, whereas in others, they are merely curiosities related to benign underlying medical conditions. In yet other cases, unanticipated biodistribution may be due to errors and blunders, colloquially termed “artifacts” in the medical imaging literature. This article focuses on identifying and understanding the clinical importance of these deviations from expected biodistribution. Abnormalities in radiopharmaceutical distribution related to focal bone pathology, the usual and intended purpose of bone scintigraphy, have not been included in this review nor are primary bone disorders such as Paget disease, fibrous dysplasia, or other similar entities that lead to regional abnormalities in MDP uptake. Abnormalities of urinary tract structure,⁶⁻⁸ a separate and specialized topic in its own right, is beyond the scope of this review.

Normal Distribution of MDP

In current practice, approximately 740-1110 MBq (20-30 mCi) of ^{99m}Tc-MDP is injected intravenously for the

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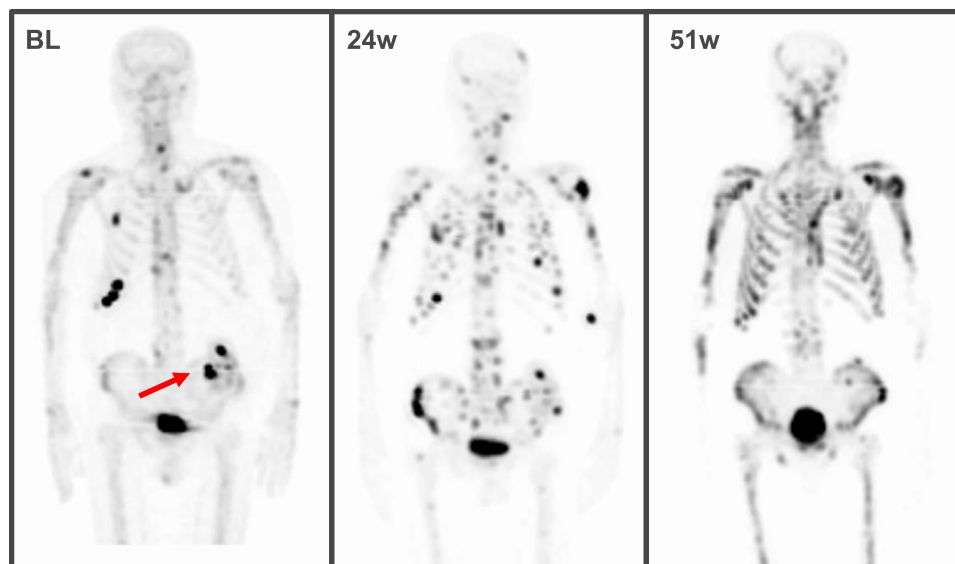


Figure 1 A 74-year-old man with castration-resistant prostate carcinoma. MDP MIP images performed at baseline (BL) and repeated at 24 and 51 weeks demonstrate progression of osseous metastases to near-confluence. Arrow indicates pelvic kidney in the left iliac fossa. At 51 weeks, the transplant renal parenchyma is not visualized and only activity in the renal collecting system is apparent. Because of the excellent bone-to-background ratio, this pattern of uptake has been described as a “superscan.” MIP, maximum intensity projection. (Color version of figure is available online.)

purpose of bone scintigraphy.⁵ Typically, imaging is performed 2-5 hours afterward to allow for clearance of the administered radiopharmaceutical from the intravascular compartment and from the extracellular nonosseous soft tissues. Plasma clearance half-time of MDP in patients with normal renal function is of the order of 3-4 minutes.⁹

A fundamental aspect of understanding the biodistribution of MDP is that it is primarily cleared by 2 pathways: renal and osseous.¹⁰ Administered MDP is partitioned according to the relative magnitude of these clearances. Therefore, the degree of osseous uptake depends not only on factors relating to bone metabolism but also on renal clearance of MDP, the latter being closely approximated by the glomerular filtration rate. Assuming normal clearance values of 40 mL/min for bone and 100 mL/min for renal, whole-body retention of MDP at 24 hours is estimated to be 30%.¹⁰

Alteration in Osseous Uptake

Diffusely Increased Osseous Uptake

Concept of the “Superscan”

Causes of diffusely increased skeletal uptake are not infrequently encountered in the routine clinic. The 2 usual etiologies of diffusely increased uptake are metastatic and metabolic disorders. Although focal increases in uptake are readily apparent on bone scintigraphy, paradoxically, it can be quite challenging to appreciate more widespread and diffuse abnormalities (Fig. 1). Bone scintigraphic images are typically windowed on a relative basis and individualized for each study, such that the average intensity of the skeleton is portrayed in the middle to upper range of gray scale. Therefore, a diffuse increase in uptake may be impossible to appreciate by inspection of the bones alone because the gray scale would have been adjusted

upward as well. Causes of widespread increased boney uptake simulating a normal appearance have been termed “superscans”¹¹⁻¹⁴ to reflect the elevated bone to soft tissue background ratio, which renders the skeleton clearly defined. Superscans have also been reported with ¹⁸F-NaF imaging.¹⁵

In a superscan, elevated skeletal activity is caused by increased osseous clearance of MDP and not by reduced renal clearance, though not infrequently, these abnormalities may coexist. Half of the total injected dosage of radiotracer is normally cleared by the kidneys,¹⁶ while in cases of elevated bone uptake, up to 86% of the radiotracer is retained in the skeleton.¹⁷⁻¹⁹ Careful scrutiny of images, with particular emphasis placed on intensity of soft tissue and urinary uptake, generally suggests aberrant uptake. Renal and bladder activity should be scrupulously assessed in all patients undergoing bone scintigraphy. Additionally, in some categories of superscan, osseous uptake may be somewhat asymmetric and inhomogenous and may differentially affect the axial and appendicular skeleton.

Superscan Due to Metabolic Disease

Superscans may result from metabolic conditions that alter the global pattern of skeletal remodeling. The pattern of uptake is unrelated to the bone marrow distribution; therefore, osseous involvement tends to be relatively diffuse and homogeneous, more accurately mimicking the normal distribution of activity within the axial and appendicular skeleton. Idiosyncratic features associated with metabolic superscans include prominent sternal activity (so-called tie sternum), beading of the costochondral junctions, and prominent uptake in the calvaria (Fig. 2) and mandible.²⁰

Endocrine disorders are an important cause of metabolic superscan, with hyperparathyroidism (primary, secondary, or tertiary²¹⁻²⁵) being most frequently implicated. Owing to the

important role played by the kidneys in the regulation of serum levels of calcium, phosphate, and 1,25-dihydroxycholecalciferol, renal disorders can lead to abnormalities in bone metabolism. Renal osteodystrophy—a blanket term that includes secondary and tertiary hyperparathyroidism, osteomalacia, mixed uremic osteodystrophy, and adynamic bone disease²⁶⁻²⁹—occurs in patients with end-stage renal disease and is a common cause of abnormal bony remodeling. Additional renal pathology associated with superscan includes distal renal tubular acidosis³⁰ and Fanconi syndrome.³¹ Other reported metabolic causes of superscan include hyperthyroidism,^{32,33} acromegaly,³⁴ hypervitaminosis A³⁵ and D,³⁶ and fluorosis.¹²

Superscan Due to Metastatic Disease

Superscans due to widespread osseous metastases occur most frequently in the context of breast^{17,37} and prostate cancer^{11,19,38,39} but may also be seen in lung,¹¹ genitourinary tract,⁴⁰ gastrointestinal (GI) tract,^{41,42} head and neck,⁴³ and occasionally hematological malignancies.^{16,18,44-47} Not surprisingly, metastatic superscans are indicators of poor prognosis.⁴⁸⁻⁵¹

The appearance of a metastatic superscan is characterized by abnormally increased skeletal uptake in a distribution similar to that of the bone marrow, that is, the axial and proximal appendicular skeleton to a greater degree than the appendicular skeleton. It is this specific distribution that allows the metastatic superscan to be distinguished from other causes of

increased bony uptake. In addition, close examination usually reveals a mildly heterogeneous appearance of the involved bone as diffuse involvement of the skeleton represents summation of innumerable foci of discrete blastic metastases.

Regional Increase in Skeletal Uptake

Hypertrophic Osteoarthropathy

In hypertrophic osteoarthropathy (HO), formally known as hypertrophic pulmonary osteoarthropathy, increase in MDP uptake is limited to the distal upper and lower extremities with a predominantly peripheral (“tram track”) periosteal appearance.⁵² Similar findings have been noted in ¹⁸F-NaF imaging.⁵³ HO may be associated with physical manifestations such as clubbing of the fingers.⁵⁴⁻⁵⁶ Several clinical disorders, especially those involving the thorax, have been linked to this condition, which are postulated to lead to common stimulatory pathways; implicated mediators include vascular endothelial growth factor, platelet-derived growth factor, platelets, and increased prostaglandin E2 levels.⁵⁴

Complex Regional Pain Syndrome

Complex regional pain syndrome, previously termed reflex sympathetic dystrophy, results in increased blood flow to a single involved extremity, which manifests as increased bony uptake of MDP on the delayed images.⁵⁷⁻⁷⁰ There is often a history of antecedent injury or neurologic insult followed by persistent pain and skin changes. On bone scintigraphy, a periarticular accentuation of activity is typically noted⁶⁰ (Fig. 3). With time, the activity seen on bone scan can normalize.

Radiation Osteitis

The progression of radiotracer uptake following irradiation was studied by King et al⁷¹ in rabbits. It was found that uptake in irradiated bone increased for the first 3 months after treatment and then decreased, eventually reaching levels lower than the baseline levels at 6 months after treatment.

In patients treated with high doses (50 Gy or more), the uptake can be intense and uniform,⁷² with abrupt changes seen at the edge of radiation ports. The uptake generally normalizes and then decreases and, in the chronic phase, bones can appear heterogeneous owing to a combination of sclerosis and ongoing remodeling interspersed with areas of necrosis and fibrous changes appearing as cold defects.

Arterial Injection of Radiotracer

On occasion, the radiopharmaceutical is inadvertently injected into an artery rather than a peripheral vein. In these cases, the downstream tissues show a concentrated bolus of MDP leading to elevated accumulation of activity based on this “first pass” of activity,⁷³⁻⁷⁶ which results in a “glove” or “hot-hand” appearance (Fig. 3). The remainder of the concentrated bolus reaches the right atrium and is diluted by the systemic return, thereafter distributing throughout the body in a typical fashion.

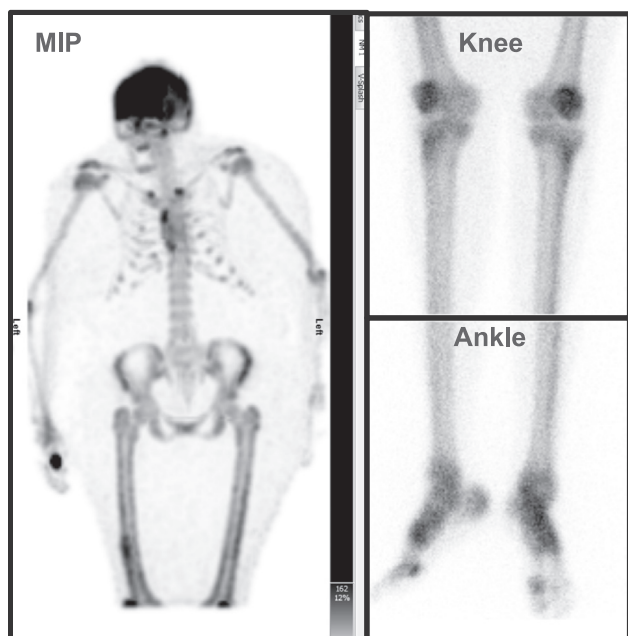


Figure 2 Metabolic superscan in a 61-year-old woman with long-standing renal failure and radiographic diagnosis of renal osteodystrophy and increased parathyroid hormone levels on dialysis. The patient underwent bone scan to evaluate ankle pain, consisting of SPECT imaging from the skull to the thighs and supplemental planar imaging of the lower legs. On MIP image, no urinary activity is seen in the kidneys or bladder, and there is intense uptake in the skull and patella. Renal osteodystrophy was confirmed. Focal uptake in the right distal femoral diaphysis was noted. MIP, maximum intensity projection.

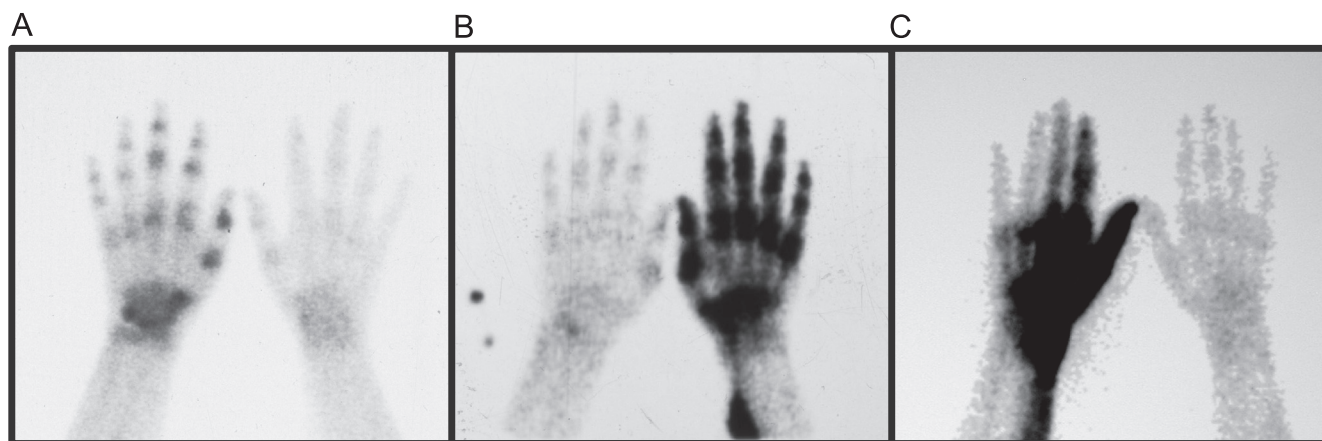


Figure 3 Images of 3 sets of hands in the palmer position. Patient A experienced persistent right hand pain following minor injury. Delayed bone scintigraphy demonstrates diffuse uptake in the affected hand, with a periarticular distribution, typical of complex regional pain syndrome. Patients B and C both received inadvertent injections into the radial arteries of the left (B) and right (C) hands. There is markedly increased osseous uptake distal to the injection site, owing to a “first-pass” effect. In patient B, the entire hand is affected whereas in patient C, the ulnar aspect of the hand is relatively spared. (Images of patient C courtesy of Jay Kikut, MD.)

Diffusely Reduced Osseous Uptake

Identifying globally reduced uptake on a bone scan can be challenging because of the role of windowing in compensating for depressed osseous uptake. As in the case of superscans, comparing osseous activity to that present in soft tissues and the genitourinary tract is essential.

Although soft tissue activity is negligible during delayed phase imaging in normal instances, in cases of diffusely reduced osseous uptake, there is persistent soft tissue activity noted. Trivial causes of poor bone-to-soft-tissue ratio distribution include interstitial injections and radiopharmaceutical errors.

Heavy Metal Toxicity

One of the few causes of a diffuse decrease in skeletal uptake of radiotracer is aluminum toxicity,⁷⁷ which is reputed to block bone mineralization through deposition at the calcification fronts, resulting in osteomalacia.⁷⁸ This pathology is most commonly encountered in patients with end-stage renal disease and has declined in incidence through the use of improved dialysis systems and the avoidance of aluminum-containing antacids. A decade ago, the incidence of elevated serum aluminum levels in dialysis patients was found to be approximately 1%.⁷⁹

Like aluminum, iron overload⁸⁰ has also been found to alter the biodistribution of MDP, with a resulting global decrease in bony uptake seen in patients and animal models.⁸¹⁻⁸³ It is speculated that the presence of iron facilitates dissociation of technetium from the carrier ligand (MDP) with a commensurate change in biodistribution.⁸⁴ Iron overload is most commonly encountered in patients with hereditary hemochromatosis and individuals receiving frequent blood transfusions.

Osteoporosis and Bisphosphonate Therapy

Reports of osteoporosis being associated with slightly decreased skeletal radiotracer uptake have appeared^{85,86}; however, this

finding is usually subtle. Etidronate, a nonnitrogenous bisphosphonate used to treat low bone mass, has also been associated with osteomalacia.⁸⁷⁻⁹⁰ Patients taking this medication while undergoing bone scintigraphy have been noted to have diffusely decreased MDP skeletal uptake.⁹¹⁻⁹⁴ At present, the use of etidronate has been superseded by other agents in the same class. The association of decreased MDP uptake with other bisphosphonates has not been demonstrated.

Regionally Decreased Radiotracer Uptake Previously Irradiated Bone

Irradiated bone demonstrates decreased radiotracer uptake in the chronic phase, occasionally with a mottled appearance. Typically, there is a sharp transition between treated and untreated bone, determined by the radiation port.^{95,96}

Electrical Injury and Frostbite

Bone scintigraphy has been used in the evaluation of nonviable bone following electrical injury.⁹⁷⁻⁹⁹ In these cases, devascularized bone appears cold on scintigraphy. It has been shown that results of bone scintigraphy correlate well with the required level of amputation. Bone scintigraphy can also be used to assess for soft tissue and bone viability following frostbite injury¹⁰⁰⁻¹¹⁰ (Fig. 4¹¹¹). Areas of absent uptake on bone scintigraphy correspond to nonviable tissue.

Alteration in Soft Tissue Uptake

It is hypothesized that MDP and its analogues bind to bone by adsorption to the surface of the hydroxyapatite crystal (“chemiadsorption”), with areas of new bone formation exhibiting elevated uptake owing to increased blood flow and expanded surface area.¹¹² Multiple etiologies of increased soft tissue uptake of MDP have also been described, which appear related to focal calcium uptake within the soft tissues; apparently, the radiopharmaceutical also binds onto the surface of the

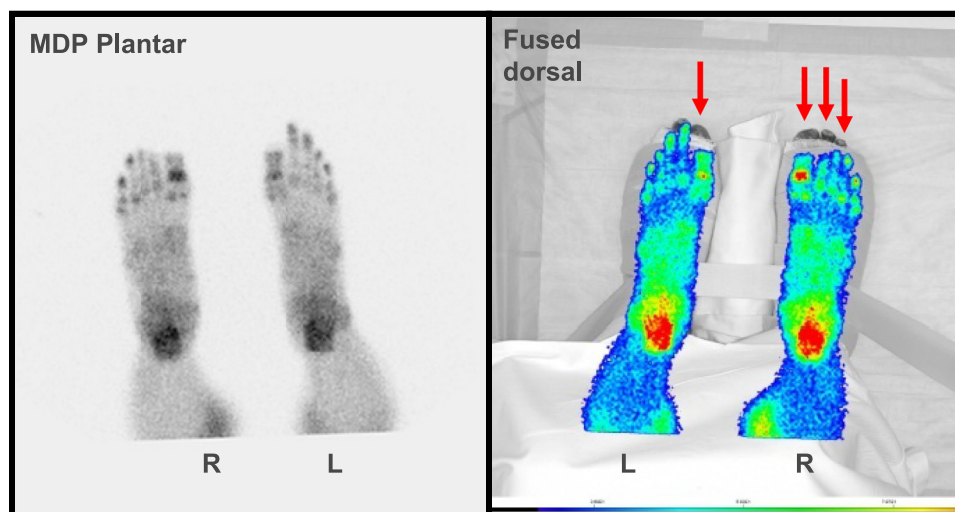


Figure 4 Homeless man with frostbite injury to the feet. MDP plantar bone scan demonstrates distribution of MDP uptake within the feet. The image has been flipped and fused with a dorsal photographic image, as previously described.¹¹¹ There is no uptake in the distal phalanges of the left first and right first and second toes as well as the tip of the right third toe, indicating lack of viability (arrows).

deposited calcium salts by chemisorption.¹¹³ Underlying processes leading to calcium and MDP deposition within the cellular compartment include metastatic calcification, dystrophic calcification, and metabolic deposition. We have illustrated and reviewed many of these processes in an earlier contribution to this journal.¹¹⁴ Another category of apparent soft tissue MDP activity is that which is not due to actual deposition of radiopharmaceutical within the tissues but rather derives due to a diminished or delayed clearance of activity from regional collections or compartments where the radiopharmaceutical is relatively sequestered, appearing prominent in comparison with the remainder of the soft tissues.

Finally, a number of blunders or other technical problems can also lead to apparent alterations in distribution of bone radiopharmaceuticals, colloquially termed “artifactual” in the medical imaging literature.

Metastatic Calcification

Metastatic calcification refers to calcium (Ca^{2+}) deposition in normal tissues subjected to hypercalcemia and is typically induced by marked and rapid rise in serum Ca^{2+} and phosphate (PO_4^-). Calcification (and MDP uptake) is said to most frequently affect tissues that tend to an alkaline pH, including lung, stomach, and kidney. In our experience, lung uptake, without concomitant gastric activity, is not infrequently encountered (Fig. 5). Systemic arteries and pulmonary veins, which also secrete acid and have an internal alkaline compartment, are also prone to metastatic calcification.¹¹⁵ Femoral artery uptake of MDP, especially in older patients, has frequently been noted^{116,117}; dystrophic changes in the vessels may also participate in this process. In some instances, MDP uptake in metastatic calcification has been shown to favor large

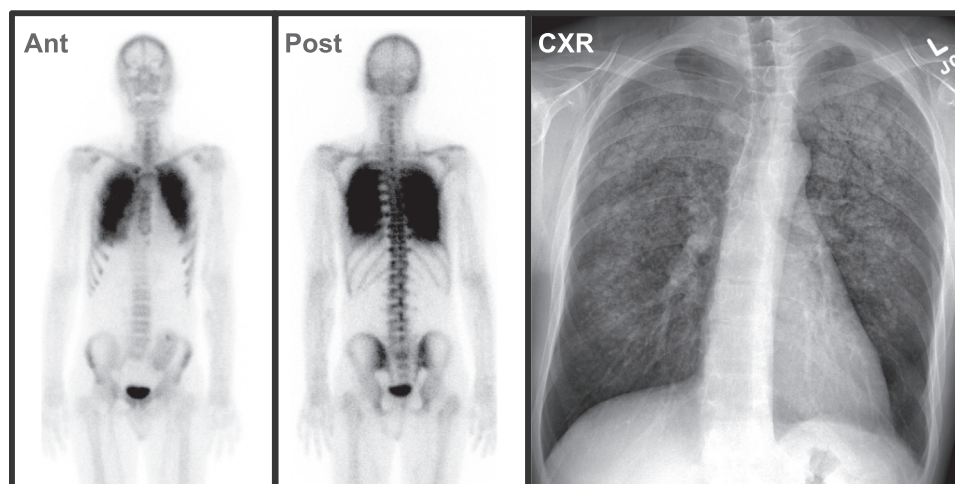


Figure 5 A 37-year-old man with previous renal transplant 15 years ago now presenting with persistent cough. Intense lung uptake of MDP on anterior and posterior images is due to metastatic calcification in renal failure. Note faint kidney in the left iliac fossa. CXR demonstrates diffuse metastatic pulmonary calcifications. CXR, chest x-ray.

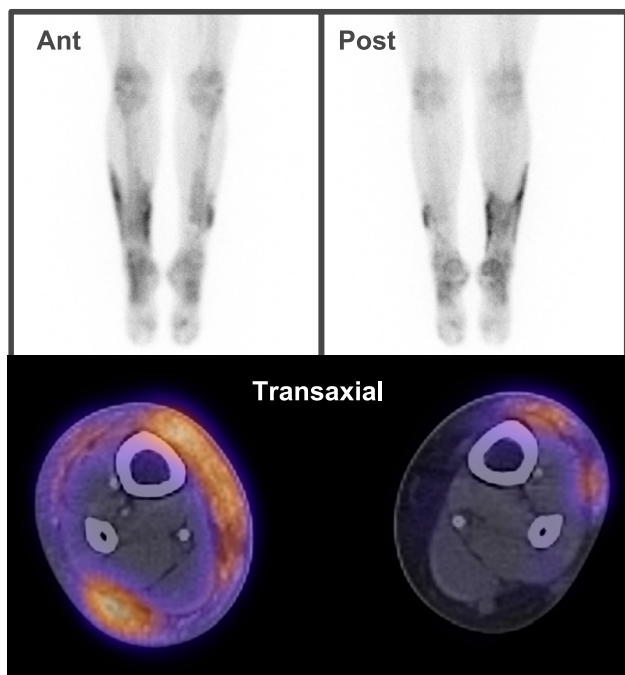


Figure 6 A 26-year-old woman on dialysis developed a rash on her legs. Bone scintigraphy in anterior and posterior projections demonstrates relatively intense uptake over her lower calves, especially in the right leg. Representative transaxial SPECT/CT image demonstrates localization of MDP primarily in the subcutaneous fat.

muscle groups of the shoulders and thighs, possibly related to chronic subclinical trauma.¹¹⁸ Calciphylaxis, often associated with tertiary hyperparathyroidism, results in systemic medial calcification of the arteries, most commonly leading to ischemia of dermis and subcutaneous fat,¹¹⁹ with typically intense uptake noted on bone scintigraphy¹²⁰⁻¹²³ (Fig. 6).

The clinical conditions associated with metastatic calcification include disorders with increased secretion of parathyroid hormone (including renal failure), destruction of bone, and vitamin D-related disorders (including sarcoidosis where macrophages activate a vitamin D precursor). Aluminum intoxication, seen in patients undergoing long-term dialysis, and milk-alkali syndrome, due to excessive intake of calcium, are less common causes of metastatic calcification.¹¹⁵ In pulmonary microlithiasis, a genetic defect leads to impaired activity of the phosphate transporter which is presumably implicated in microlith formation by metastatic calcification^{124,125}; intense MDP uptake has been described in this condition^{126,127} (Fig. 7). Interestingly, while a similar abnormality may be present in testicular microlithiasis, we are not aware of scintigraphic imaging having been described in this disorder.^{124,128}

Dystrophic Calcification

Dystrophic calcification occurs in patients with normal Ca^{2+} and PO_4^- levels and refers to Ca^{2+} deposition in tissues secondary to histologic disruption caused by trauma, ischemia, or cellular necrosis or in the enzymatic necrosis of fat. Ca^{2+} is

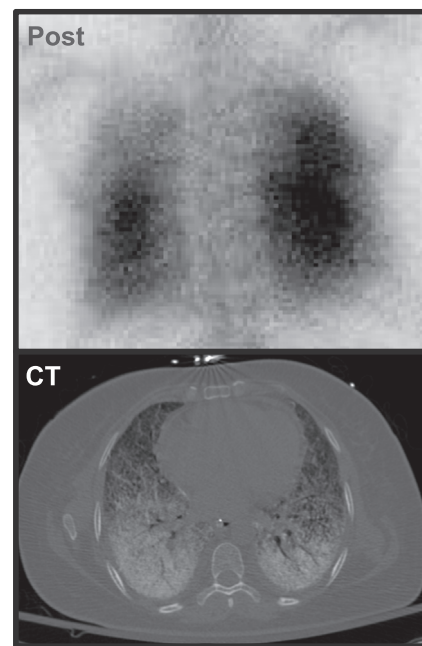


Figure 7 Intense pulmonary uptake of MDP in pulmonary microlithiasis in a 57-year-old woman. Posterior scintigraphic view of the chest demonstrates intense homogeneous lung uptake, while transaxial unenhanced CT demonstrates confluent pulmonary calcifications.

thought to bind to phospholipids present in membrane-bound vesicles, phosphatases generate phosphate groups, which in turn bind to the calcium, and the cycle is repeated until local concentrations are elevated and crystals begin to form.¹¹⁵ Hyaline collagen degeneration, a consequence of tissue damage, is particularly associated with Ca^{2+} deposition.¹²⁹

Examples of dystrophic calcification which are often associated with MDP uptake include infarctions of the brain, heart, and muscle, including uterine myomata.¹³⁰ Overexertion of skeletal muscle has also been associated

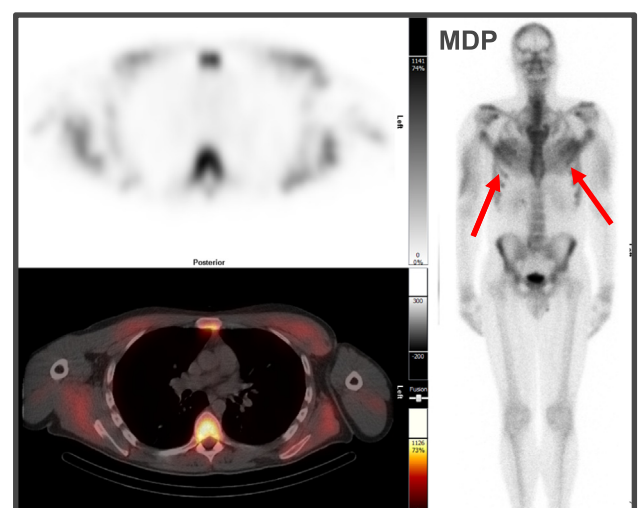


Figure 8 SPECT/CT images of a young man with MDP uptake within muscles of his upper trunk following strenuous exercise. The pectoralis muscles are prominently visualized (arrows).

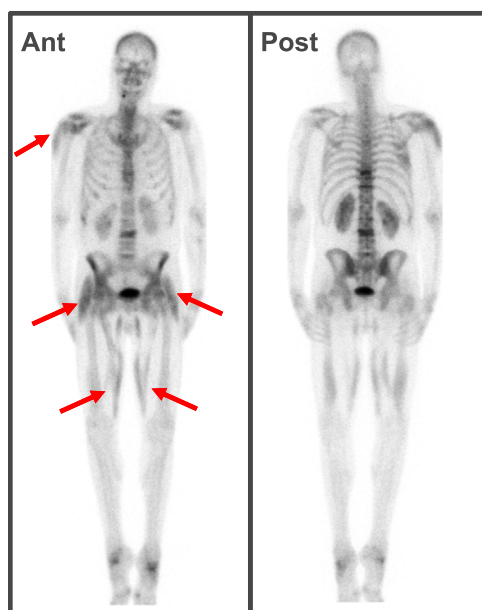


Figure 9 Anterior and posterior MDP images of a 48-year-old man with a brain tumor. Recent seizure resulted in multiple fractures of the thoracolumbar spine. In addition, uptake of MDP in the right deltoid and muscles of the legs bilaterally (arrows) is consistent with soft tissue injury after seizure.

with MDP uptake, presumably owing to mild degrees of damage and necrosis¹³¹ (Figs. 8 and 9). Splenic uptake may be observed in autoinfarction associated with sickle cell anemia (“autoinfarction”) ¹³²⁻¹³⁴ (Fig. 10), but it can be due to other causes, such as lymphoma, as well.¹³⁵ Dystrophic calcification is likely the mechanism of uptake

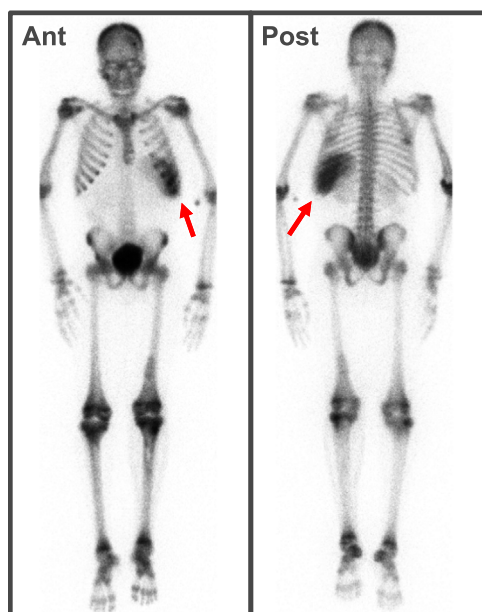


Figure 10 An 18-year-old with sickle cell anemia. Characteristic findings include prominent activity in the calvarium and at the end of long bones due to marrow expansion, as well as intense activity within the spleen, consistent with autoinfarction, related to dystrophic calcification.

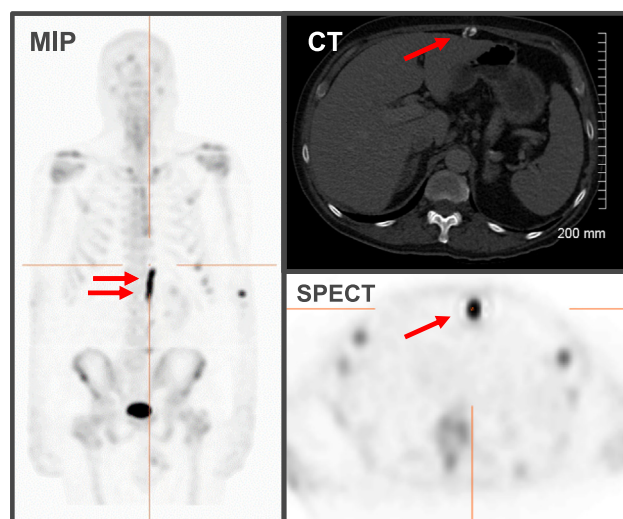


Figure 11 A 76-year-old man with renal carcinoma who underwent right nephrectomy. Anterior MIP image, CT scan, and SPECT scan demonstrate intense MDP uptake and dense calcification corresponding to scar in the anterior abdominal wall (arrow). MIP, maximum intensity projection.

in deep vein thrombosis^{136,137} and phlebitis.¹³⁸ Uptake in injection sites,^{139,140} scars^{141,142} (Fig. 11), and in soft tissue diseases such as dermatomyositis¹⁴³ is likewise due to dystrophic calcification. Although historically iron dextran is implicated in MDP uptake in injection granulomata,^{139,140} more common causes of injection-related uptake today include subcutaneous injections of heparin¹⁴⁴⁻¹⁴⁶ and other medications that induce inflammation¹⁴⁷ (Fig. 12).



Figure 12 Anterior and posterior whole-body images demonstrate a symmetric pattern of MDP uptake (arrowheads) in the shoulders, anterior abdomen, and thighs in a 16-year-old girl receiving rotating subcutaneous injections of enfuvirtide (FUZEON), a peptide that interferes with fusion of HIV to host CD4 cells. HIV, human immunodeficiency virus. (Reprinted with permission from Pack and Zuckier.¹⁴⁷)

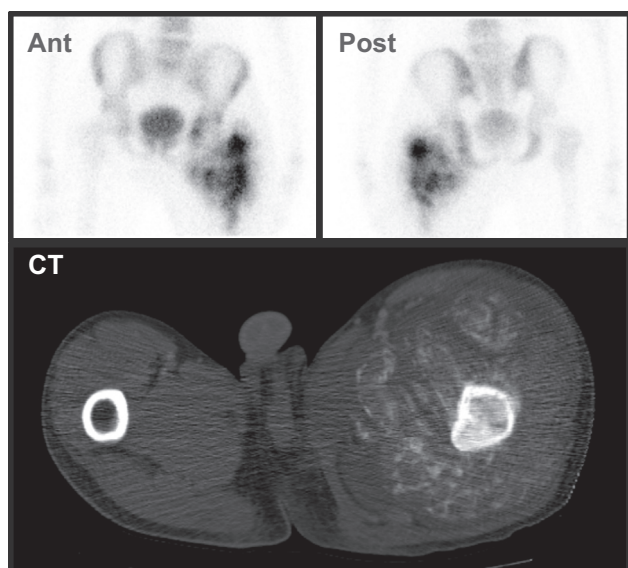


Figure 13 Anterior and posterior planar MDP images and transaxial CT image of the left hip in an 18-year-old male patient with osteosarcoma of the proximal left femur. Avid MDP uptake corresponds to presence of primary tumor; there was no scintigraphic evidence of metastatic spread.

Metabolic Calcification

Several metabolic mechanisms lead to formation of bone, and in turn, uptake of MDP. Osteogenic sarcoma metastases produce an osteoid matrix that binds MDP (Fig. 13).

In a similar manner, myositis ossificans represents a dedifferentiation of muscle into osteoid-producing tissue (Fig. 14).

Mucin-producing tumors possess a glycoprotein that is biochemically similar to ossifying cartilage and binds Ca^{2+} salts. Classically, mucinous adenocarcinoma tumors of the lung, breast, GI tract, and ovary¹⁴⁸⁻¹⁵¹ are associated with MDP uptake, although it may also be seen in tumors with other histology. In addition to uptake in the primary tumor, activity may also be noted in metastases within lymph nodes, lung, and liver.¹⁵² Rarely, MDP-concentrating metastases are disseminated in the soft tissues¹⁵¹ (Fig. 15). Pathologic uptake in breast, secondary to malignancy such as adenocarcinoma,¹⁵³ should be differentiated from normal physiological uptake,¹⁵⁴ which is generally symmetric, mild, and often prominent in the young postpubescent population. So too, fibrils of amyloidosis are said to have a physiological affinity for calcium,¹²⁹ although the exact mechanism of uptake of MDP in amyloidosis is not known.^{155,156} Tumor uptake is also frequently observed in neuroblastoma, related to an intrinsic metabolic characteristic of the tumor.

Certain tissues that calcify over time, such as thyroid cartilage, can exhibit MDP uptake as a normal variant.¹⁵⁷ In the past, bone scintigraphy has been used to follow up vascularization of eye prostheses,¹⁵⁸ also reflecting physiological deposition onto hydroxyapatite. Meningiomas are known to calcify and frequently take up MDP¹⁵⁹⁻¹⁶¹ (Fig. 16).



Figure 14 Anterior and posterior planar MDP images and plain film radiograph of the left hip in 20-year-old woman with a painful mass, which was determined to be myositis ossificans (arrow). Onset of pain and formation of mass followed minor local trauma. (Color version of figure is available online.)

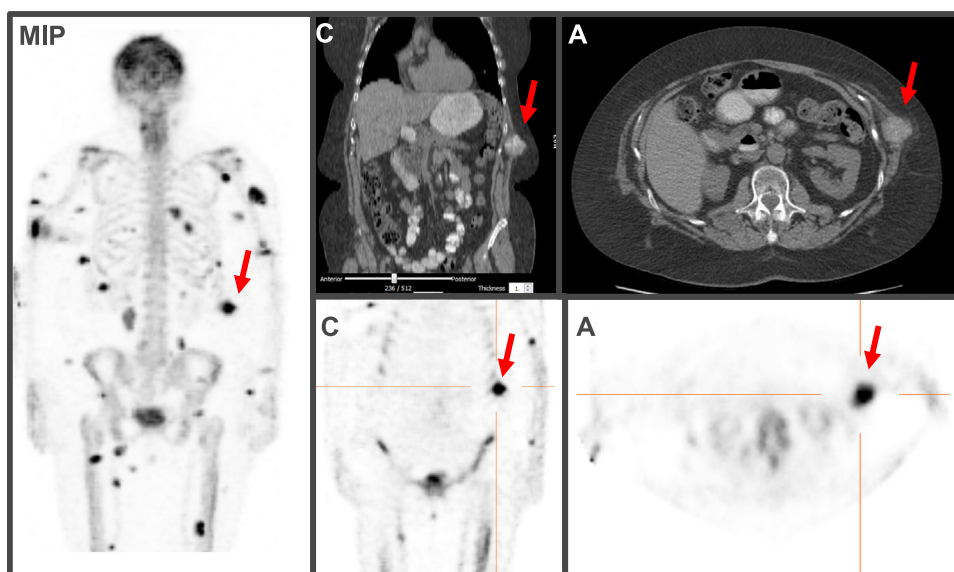


Figure 15 Anterior MIP image in a 52-year-old woman with a medical history of stage IIIC ovarian mucinous adenocarcinoma, treated with surgery and chemotherapy, who returned 10 years later with innumerable MDP-avid soft tissue metastases, proven to be recurrences. Coronal (C) and transaxial (A) images from CT (upper panel) and MDP study (lower panel) demonstrate correlation of focal FDG uptake in muscle with calcified metastasis (arrow). Other MDP-avid lesions were located in the subcutaneous fat. MIP, maximum intensity projection. (Modified with permission from Sogbein et al.¹⁵¹)

Sequestration

In some situations, MDP in soft tissues is present to an extent greater than in the background, not due to active accumulation in soft tissues, but rather, to a slower transit or washout from that region or compartment as compared to neighboring tissues. For example, venous or lymphatic obstruction may lead to an expanded extracellular space within an edematous extremity, with a reduced rate of clearance compared with the remainder of the body (Fig. 17). In this situation, a relative

localized increase in activity is apparent on delayed bone-phase imaging, as clearance of the radiopharmaceutical in the affected extracellular space lags behind that of the remainder of the body.¹⁶² So too, pleural effusions and peritoneal ascites¹⁶³ (Fig. 18) may be associated with uptake of MDP, a finding that correlates with exudative etiology and likelihood of malignancy.¹⁶⁴⁻¹⁶⁶ Excessive capillary permeability (typically seen in malignant effusions¹⁶⁷) permits rapid permeation of the radiopharmaceutical into the effusion when blood

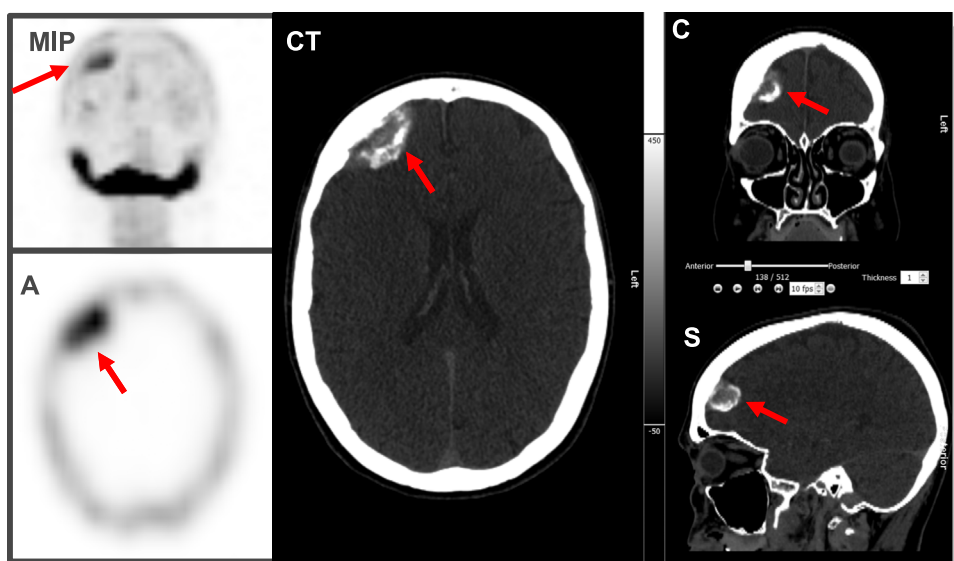


Figure 16 In the course of bone scintigraphy performed to evaluate the mandible, which was demonstrated to be pagetoid, an incidental area of intracranial MDP uptake was noted adjacent to the inner table of the right frontal bone (arrows), seen on anterior MIP and transaxial (A) scintigraphic images. Orthogonal CT images in transaxial (CT), coronal (C), and sagittal (S) planes through the lesion are typical of a calcified meningioma. MIP, maximum intensity projection.



Figure 17 Anterior and posterior bone scintigraphic images in an 80-year-old woman with breast cancer demonstrate evidence of osseous metastatic disease. In addition, there is right arm swelling, with increased soft tissue activity, which correlated with known acute obstruction of the right subclavian vein. Bone scan performed 3 months earlier did not demonstrate abnormality of the arm.

concentration of the radiopharmaceutical is high. The relatively large pleural-fluid distribution volume results in slow back diffusion, resulting in a relatively higher concentration in the effusion than in other soft tissues at the typical time of imaging.¹⁶⁴⁻¹⁶⁶

Metastases to the brain frequently cause breakdown of the blood-brain barrier, and this phenomenon was exploited in early scintigraphic brain scanning,¹⁶⁸⁻¹⁷⁰ which images radiopharmaceutical after passive leakage into the brain. Uptake of MDP within brain metastases represents a combination of this leaky blood-brain barrier phenomenon and potentially, actual accretion of MDP into the tumor via dystrophic calcification or metabolic uptake mechanisms¹⁷¹ (Fig. 19).

Visualization of bowel activity following bone scans in patients with primary intestinal lymphangiectasia¹⁷² or protein-losing enteropathy¹⁷³ can be understood as visualization of MDP-bound plasma proteins that have extravasated into the bowel and become sequestered from the circulation. Likewise, the rare occurrence of frank GI bleeding following the injection of MDP results in the trapping of radiopharmaceutical within the bowel lumen.¹⁷⁴ A recent report has shown the administration of intravenous iodinated contrast between the injection and imaging of MDP to be related to bowel visualization in a high proportion of patients.¹⁷⁵ Although the mechanism involved in this process is not clear, this observation may be useful in explaining previously cryptic cases of bowel MDP uptake (Fig. 20).

On occasion, radiolabeled urine may communicate with neighboring structures owing to fistulous connections,¹⁷⁶ as noted in renal, bladder, and bowel tumors (Fig. 21), or

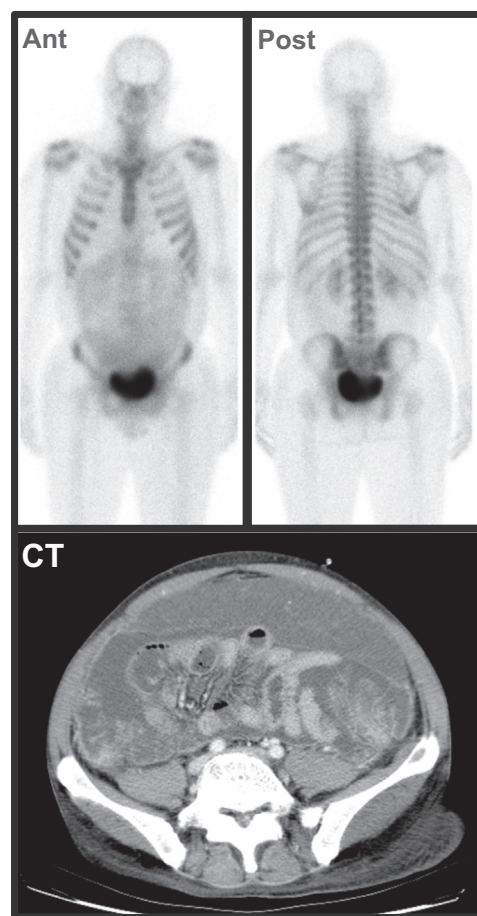


Figure 18 Anterior and posterior images following bone scintigraphy in a 31-year-old man with severe peritoneal carcinomatosis from unknown primary tumor. MDP-containing ascites is noted at time of imaging. CT scan demonstrates centralization of the bowel within the large amount of ascites.

following surgically created urinary diversions that incorporate loops of bowel.¹⁷⁷ Finally, in certain cultures, self-ingestion of urine is believed to have medicinal properties; in such cases, stomach, small intestine, or bowel uptake may be noted due to radiopharmaceutical-containing urine.¹⁷⁸⁻¹⁸¹

Infiltrated injections of radiopharmaceutical may result in uptake within draining lymph nodes.¹⁸²⁻¹⁸⁵ In these cases, documentation of the injection site, or imaging of the extremity distal to the node, may be helpful in explaining the cause of this finding. Chatterton has postulated that extravasated radiopharmaceutical results in colloid formation, which in a sense is sequestered in the draining lymph node; faint liver uptake of colloid may occur as well.¹⁸³

Spurious Uptake

As imaging becomes less centralized and smaller imaging centers have opened, the potential for interference between previously administered radiopharmaceuticals and imaging of current radiopharmaceuticals has increased. These relatively common and etiologically trivial causes of unusual uptake should be considered early in the differential diagnosis of altered biodistribution. There may be visualization of the

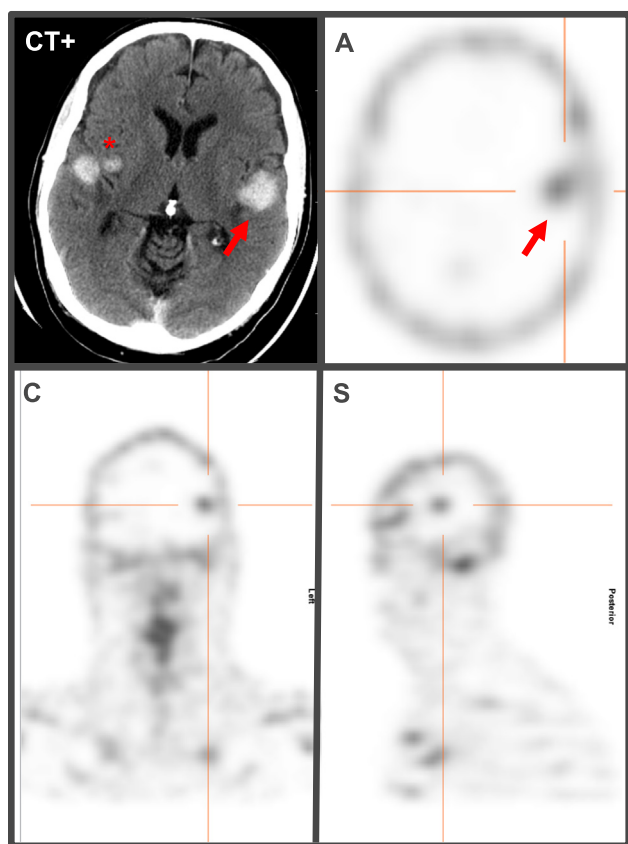


Figure 19 MDP uptake in 3 orthogonal planes through the skull in a brain metastasis located in the left hemisphere in a 67-year-old male with small cell lung cancer. Enhanced CT scan was performed 5 days before the bone scan and demonstrates additional lesions in the right hemisphere (*) that are not identifiable on bone scintigraphy.

liver and spleen following prior marrow-imaging study or visualization of the colon following an earlier cardiac ^{99m}Tc -sestamibi perfusion study. These ^{99m}Tc -labeled compounds typically remain visible for usually no more than 1 day after administration because of the 6-hour half-life of ^{99m}Tc . On the contrary, radiopharmaceuticals incorporating longer-lived radionuclides are apparent for more extended periods of time, depending on their physical and biological clearance. For example, ^{131}I -NaI may remain visible following thyroid ablation for months because of the large dosage, long physical half-life, and prolonged biological half-life. Inefficient collimation of the energetic 364-keV photons results in septal penetration and poorly defined appearance of the activity within the neck.

Radiopharmaceutical impurities can also cause apparent soft tissue uptake. Free pertechnetate, if present in the bone radiopharmaceutical preparation, is concentrated in the stomach and thyroid.¹⁴¹ Reduced hydrolyzed technetium, which can arise from errors in constituting radiopharmaceutical kits or due to excess aluminum ion,^{186,187} results in colloid formation and activity accumulating within the liver and spleen. Technetium may also exist in other chemical forms that are excreted by the liver into the biliary tree and bowel, though the exact mechanism of origin of the contaminant in these cases may not be clear.¹⁸⁸⁻¹⁹⁰ In a hospital's experience, moderate to intense bowel uptake, usually in the ascending colon, was noted in approximately 1% of 2144 cases studied over a period of 18 months.¹⁹⁰ The incidence of gall bladder or bowel visualization may reach 5%-10%.¹⁹¹ These statistics cannot be generalized as the frequency of radiopharmaceutical-based uptake depends on the specific source of reagents and particular technique used at each radiopharmacy.

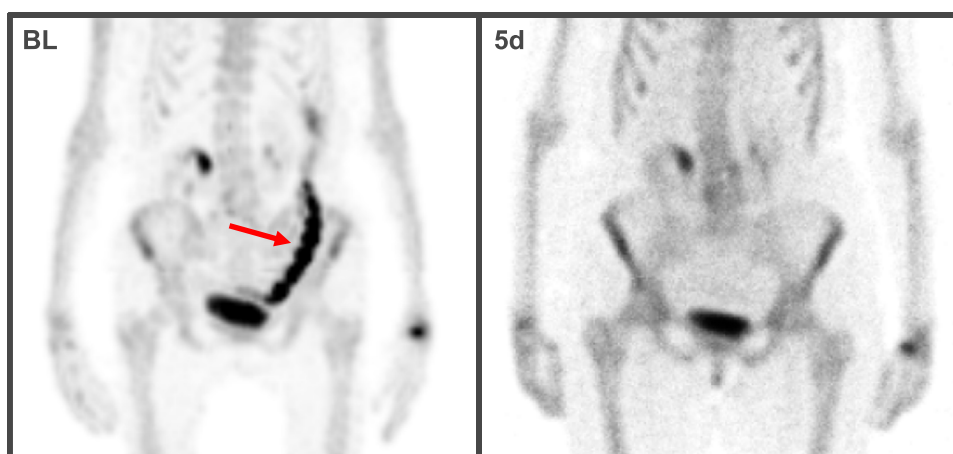


Figure 20 Initial planar baseline (BL) and repeat MIP study performed after 5 days (5d) demonstrate relatively intense bowel uptake seen on the initial but not repeat study (arrow). The patient had not undergone a prior nuclear medicine study nor was any other etiology of bowel uptake elicited. In retrospect, this finding is consistent with reported effect of IV contrast administration following radiopharmaceutical administration; MDP was administered at 8:45 AM and CT contrast was injected 30 minutes thereafter. Incidental note made of horseshoe kidney. IV, intravenous; MIP, maximum intensity projection.



Figure 21 Anterior and posterior bone scintigraphic images of a 60-year-old man with prior history of colorectal carcinoma treated with external beam radiation. Intense bowel activity is secondary to known colovesicular fistula.

Conclusion

With extensive experience in bone scintigraphy using single-photon radiopharmaceuticals, an extensive literature of altered biodistribution has developed. Conditions that lead to altered radiotracer uptake run the gamut from benign to malignant, congenital to posttraumatic. The key to determining the etiology of abnormal osseous uptake is a combination of clinical history and careful observation of the particular pattern of radiotracer activity. Being cognizant of these unexpected abnormalities and understanding their etiology will prepare the reader to more readily appreciate the significance of these findings when encountered in clinical practice.

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