
Editorial Comment: Extra-Skeletal Uptake of Bone Agents

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The nuclear medicine literature is rich with reports of both normal and abnormal accumulation of bone imaging agents (^{99m}Tc -HDP, MDP or PYP) in extra-skeletal structures. The cases published in this issue of the *Journal of Nuclear Medicine Technology* are excellent examples of this phenomenon. Extra-skeletal uptake is usually an incidental finding on the bone scan, although the bone scan occasionally can be done for the specific diagnostic intent of identifying extra-skeletal uptake. It is important for the nuclear medicine professional to be aware of the more common conditions that can present with extra-skeletal uptake of the ^{99m}Tc bone agents. For a comprehensive listing of conditions associated with extra-skeletal uptake, the reader is referred to Dr. Datz's excellent textbook (Datz FL. *Gamuts in Nuclear Medicine*, 2nd ed. Norwalk, CT: Appleton and Lange; 1987:97–132).

Technetium-99m bone agents, pyrophosphate (PYP) and the newer generation diphosphonates (HDP, MDP) are small molecules that diffuse freely in the interstitial fluid, being available for uptake by most tissues in the body. Intravenously injected tracer first distributes in the interstitial fluid then localizes in bone, while the lymphatic system and blood stream gradually clear excess tracer from the interstitial space, with excretion by glomerular filtration. Clearance of the tracer by the kidneys is more efficient with MDP and HDP than with PYP. For this reason, when a bone scan is done for the express purpose of visualizing extra-skeletal structures, PYP often is used because it is available for uptake by soft tissues for a prolonged period of time.

Sites of extra-skeletal involvement can be seen in normal circumstances. Mild generalized soft-tissue uptake, symmetric kidney uptake, and bladder uptake are normal findings. An absence of soft-tissue and kidney uptake, hence a "superscan" or "beautiful bone scan," may indicate diffuse underlying skeletal pathology, such as metabolic bone disease or diffuse metastatic disease. However, this finding can occur in normal individuals when the time from injection to imaging is delayed longer than 4–5 h.

Abnormal extra-skeletal uptake may be focal, within a specific organ or structure, or diffuse. Diffuse uptake may occur

throughout the entire body, or within a specific extremity or region. Diffusely increased uptake throughout the body can indicate an increase in the extra-cellular volume of distribution of the tracer, such as with diffuse edema or anasarca. This finding also can indicate a decrease in clearance of the tracer from the kidneys, such as with renal failure or dehydration, or when a patient is imaged too soon after injection. Delayed (mineral phase) images should not occur earlier than 2 h postinjection. Additional delays may be required in patients who are poorly hydrated or who have renal failure. Intentional early imaging (tissue or blood-pool phase imaging) may be performed to identify sites of hyperemia. This strategy also has been used to enhance identification of soft-tissue tumors or areas of inflammation.

Diffuse uptake of the tracer in a specific extremity or region usually indicates vascular obstruction, either venous or lymphatic. In these cases, there is often accentuation of the skin. In contrast, chronic venous insufficiency of the lower extremities usually presents as mild diffuse uptake, poor definition of the underlying bones, but lack of skin accentuation. Accentuation of the skin of the breast can be seen with obstruction of the dermal lymphatics by underlying breast cancer, a finding of similar significance to skin thickening on mammography. Skin uptake of bone agents also can be seen with inflammatory, desquamative or exudative dermatologic disorders.

Focal uptake in extra-skeletal sites has a broad differential, depending on the organ or structure involved. Any heavily calcified structure in the body can take up the bone tracer. Larger structures will be more visible than small structures. However, intense bone tracer uptake can be seen in a variety of conditions in which no visible calcification is evident by plain film or CT.

Radiopharmaceutical problems can cause extra-skeletal uptake of bone agents. Free ^{99m}Tc -pertechnetate characteristically results in uptake in the stomach, bowel, salivary glands, thyroid and, occasionally, choroid plexus. It often will demonstrate a "high background" of blood-pool and diffuse soft-tissue activity as well. The formation of colloid particles of ^{99m}Tc , which can result from crumbling of the ^{99}Mo alumina column (a form of "aluminum breakthrough"), can result in diffuse liver and spleen uptake when the size of the particles is less than $1\ \mu\text{M}$, or lung uptake when the particles are larger. Of course, the recent

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administration of another organ-specific radiopharmaceutical, such as ^{99m}Tc -MAA, sulfur colloid or DMSA, must always be considered when patients display unexpected extra-skeletal uptake on a bone scan, especially when those patients were transferred recently from another hospital or clinic.

Contamination of skin or clothing with a radiopharmaceutical or urine is a common cause of extra-skeletal uptake of the bone tracer. A radiopharmaceutical that is extravasated into the subcutaneous tissues on injection may localize in regional lymph nodes on delayed images. Urine may be eliminated by removal of contaminated clothing and cleansing of the skin. Urine contamination is most marked in the perineal region, but can occur in surprising sites, particularly in the demented or pediatric patient.

Within the pelvis, there are other causes for unexpected extra-skeletal uptake on the bone scan. Tampons often are contaminated with labeled urine, producing linear uptake in the female pelvis. Bladder diverticula, or neo-bladders, may produce uptake in unusual configurations. Heavily calcified uterine fibroids can take up a bone agent. Fibroids often are very hyperemic on early vascular-phase images. This finding should not be construed as indicative of gynecological malignancy. In men, penile prostheses may develop a capsulitis, producing uptake along the margins of the prosthesis on bone scan. This mechanism likely is similar to the capsulitis, or reactive fibrosis, which can calcify and produce uptake around breast prostheses.

Uptake of a bone tracer in a muscle can indicate either acute muscle injury or myositis ossificans. The uptake in acute injury of muscle, either skeletal or myocardial, may be due to an alteration in calcium channel flux of muscle cells. This can result from injuries of many types, including trauma, ischemia, viral myositis, auto-immune myositis or electrical injury. Uptake in myositis ossificans and other types of heterotopic ossification differs in intensity as a function of the level of immaturity of the ossification process. Actively-forming heterotopic ossification will be "hot" on the early angiographic images, as well as delayed mineral phases, while mature heterotopic bone is characterized by an absence of hyperemia, and delayed uptake in proportion to bone mass.

The deposition of heavy metals in specific organs can result in accumulation of the bone agent in these organs. Heavy metals will bind ^{99m}Tc , which is the mechanism by which ^{99m}Tc is attached to most molecules for the purposes of imaging. Renal failure patients are at risk for aluminum deposition. This results from treatment with phosphate-binding antacids that contain aluminum and leaching of aluminum from the hardware components of the dialysis machinery. In addition to poor bone uptake and accentuation of anterior rib ends due to aluminum-induced osteomalacia, aluminum in the liver and spleen can be associated with uptake of the bone agent in these organs. Deposition of other metals, such as copper (Wilson's disease) and iron (hemochromatosis and hemosiderosis), also can result in uptake of bone agents in the liver and spleen. Recent chemotherapy with a variety of agents can result in mild diffuse uptake of tracer in the liver on the bone scan. Uptake of a bone agent in the spleen characteristically occurs in patients with

sickle-cell disease with "auto-splenectomy" and calcification of the spleen.

Metal deposition in the kidney often results in hot kidneys on the bone scan, which is symmetric and cortical in distribution. Mercurial diuretics were able to produce this pattern, now primarily of historic interest. Today this finding is seen most commonly after recent treatment with cisplatin.

In addition to heavy metals, the deposition of abnormal protein in specific organs can result in accumulation of bone agents in these structures. This may be caused by abundant sulfhydryl groups, which may strip and bind the ^{99m}Tc -Sn complex. This finding is best illustrated by amyloidosis, which can result in uptake of the bone agent in any organ involved with the disease. Deposition of even relatively small amounts of protein, such as myoglobin or hemoglobin in the renal tubules as is seen with myositis or hemolysis, can result in significant uptake of the bone agent in the kidneys. This same pattern of kidney uptake can be seen in massive tissue damage of other types, as with scorpion bites or massive tumor lysis due to chemotherapy. The unilaterally or bilaterally hot renal cortex must always be considered in light of potential obstruction, either of the renal vein or the collecting system. Absence of a prominent collecting system makes obstruction less likely but does not rule out a completely obstructed system, particularly that which is acute. Recent radiation to a kidney is another cause of increased cortical uptake of tracer.

Cancer also can result in extra-skeletal uptake of bone agents in ways other than those described above. Any tumor mass, either primary or metastatic, can result in uptake of the bone agents. The mechanism for this phenomenon is likely multifactorial, and includes active osseous formation, such as with osteosarcoma mets to the lung. Necrosis with dystrophic calcification, inflammation with capillary leak, and hyperemia also have been postulated as causing bone tracer uptake in soft-tissue tumors. Focal uptake in brain metastases likely is due to a focal breakdown of the blood-brain barrier, since brain uptake also is seen in acute and subacute stroke. Uptake in the liver metastases is usually focal, but can be relatively uniform with diffuse metastatic disease. The latter, as can be seen with breast cancer metastases to the liver, cannot be distinguished from the diffuse uptake resulting from chemotherapy. Uptake in lung tumors is usually focal. Uptake of bone tracer in fluid within pleural fluid or ascites indicates an exudative collection caused by tumor or infection.

Although a mild amount of symmetric uptake is common in the glandular tissue of the breasts of premenopausal, or hormone-replaced postmenopausal women, intense or asymmetric breast uptake on bone scan can be caused by breast cancer and should be evaluated. This is also true of uptake in the skin of the breast (see above). Uptake can be seen around implants (see above), and in benign serous fluid collections after mastectomy. Nonmalignant inflammation, such as mastitis, also can cause uptake on bone tracer in the breast. We have observed left breast uptake in a woman who had undergone a recent lengthy coronary angiogram and stent placement, with presumed radiation-induced inflammation.

As noted above, diffuse lung uptake on a bone scan can be

caused by a recent VQ scan or by the formation of large colloid particles due to aluminum breakthrough. Amyloidosis and a malignant effusion also should be considered in the differential. Additional etiologies for diffuse lung uptake include heavily calcified pleural plaques, and widespread calcifications due to pulmonary alveolar microlithiasis or old histoplasmosis. Patients with hypercalcemia due to primary or secondary hyperparathyroidism can display uptake of bone tracer in a variety of organs, either singly or multiply. The organs most commonly involved are the lungs, heart, stomach and pancreas. This same pattern can be seen with paraneoplastic syndrome associated

with secretion of a parathormone-like peptide. In these cases, hypercalcemia is often, but not invariably, present. These findings are not associated with visible calcification on x-ray or CT. The bone scan findings revert to normal within days of treating the cause of the disorder.

Although the bone scan remains one of the most sensitive and cost-effective imaging modalities for skeletal disorders, it also can provide valuable “free” information regarding the soft tissues. Success in these cases requires attention to subtle and unexpected findings, and a knowledge of the myriad of factors that can affect uptake of bone agents in extra-skeletal tissues.