Uptake of Technetium-99m MDP in Primary Amyloidosis with a Review of the Mechanisms of Soft Tissue Localization of Bone Seeking Radiopharmaceuticals

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CLINICAL HISTORY

A 70-yr-old retired male farmer presented with a 2-yr history of progressive low back pain. In the 4 mo prior to admission he also complained of associated lumbar and thigh stiffness causing progressive difficulty with ambulation. Past medical history included previous myocardial infarction and coronary artery bypass graft in January 1991. There was no history of back injury, peripheral joint symptoms, neurological deficit or skin rashes.

Physical examination revealed a well nourished man in no acute distress. He was afebrile with stable vital signs. General physical examination was normal. Musculoskeletal examination revealed mild thoracic kyphosis and decreased lumbar range of motion. Range of motion in the hips and shoulders was bilaterally restricted. Neurological findings including deep tendon reflexes were normal.

Multiple examinations had been performed over the previous 4 mo. A complete blood count, electrolytes, protein electrophoresis, thyroid function and liver function tests were normal. Erythrocyte sedimentation rate was 4 mm/hr and creatine phosphokinase (CK) was normal at 29 units/liter.

Radiographs of the lumbar spine were normal; osteopenia and mild kyphosis were noted in the thoracic spine. Both a previous computed tomography (CT) scan and admission CT scan of the lumbar spine failed to reveal the etiology of symptoms. A bone scan and gallium scan performed during the current admission demonstrated abnormal soft tissue accumulation of ^{99m}Tc-methylene diphosphonate (MDP) and ^{67}Ga citrate within musculature surrounding the shoulders and proximal femora. Abnormal localization of ^{99m}Tc-MDP was also noted in the thigh musculature and the paraspinal muscles around L3 and L4 (Figs. 1A, 1B). The bone scan was used to direct magnetic resonance imaging (MRI) of the shoulders, lumbar spine and proximal femora. A selected transverse section from a T2-weighted MR images demonstrates diffuse increased signal intensity in the proximal adductor and quadriceps musculature in both thighs (Fig. 2). Abnormal signal intensities also were noted in the lumbar paraspinal muscles and in the rotator cuff musculature bilaterally. The MRI findings were compatible with polymyositis, although serum CK and electromyography were normal.

Pathological Findings

Biopsy of the left adductor muscle was performed. Hematoxylin and eosin-stained paraffin and frozen sections showed variation in fiber size with occasional degenerating fibers and perivascular infiltration suspicious for amyloid deposits (Fig. 3). No inflammation was present. Congo red staining revealed green birefringent amyloid deposits in the thickened walls of microvessels and occasionally in the interstitium around individual muscle fibers. These findings were interpreted to indicate primary amyloidosis.

DISCUSSION

Amyloidosis is a rare disorder characterized by variable intracellular accumulation of a complex substance consisting of proteinaceous fibrils (amyloid fibrils) and nonfibrillar glycoprotein or amyloid P component (*1,2*). Amyloid deposits can be found in almost any organ of the body and are most commonly perivascular.

The first report of bone-seeking radiopharmaceutical localization in amyloid was reported by Van Antwerp (*3*). More recently, scintigraphic imaging of amyloid has been accomplished with both iodinated serum amyloid P com-

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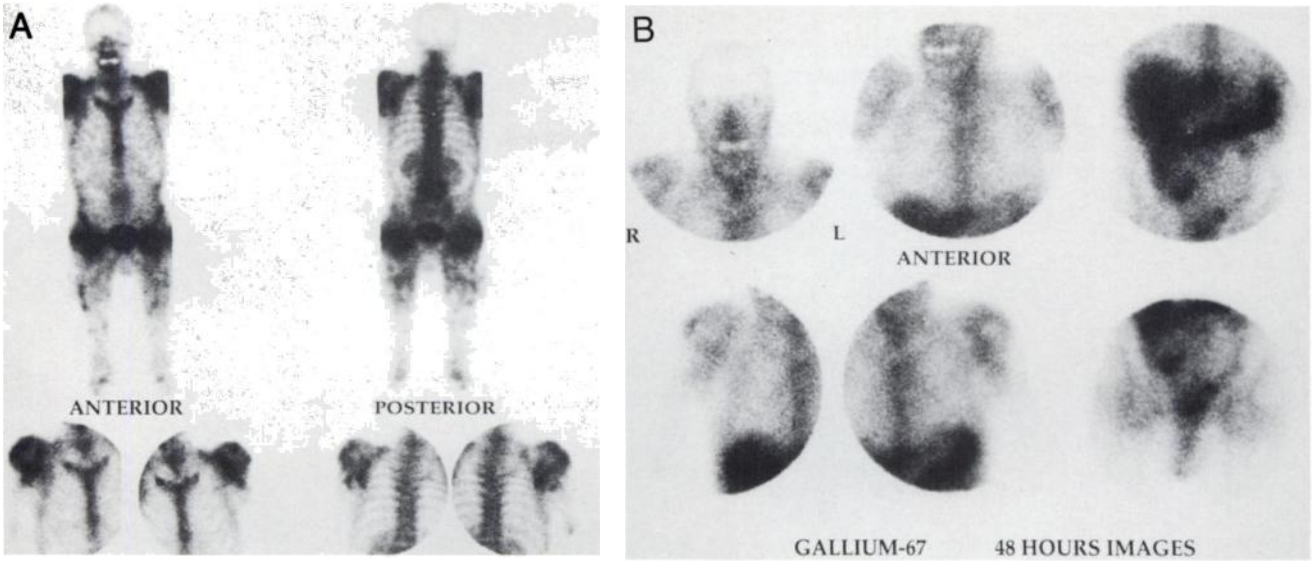

FIGURE 1. (A) Bone scan performed 3 hr following the intravenous administration of ^{99m}Tc-MDP and (B) corresponding images obtained 48 hr following the injection of ^{67}Ga citrate demonstrate abnormal soft tissue accumulation within the musculature surrounding the shoulders, proximal femora and mid lumbar spine.

ponent and beta-2-microglobulin as well as ^{99m}Tc-dimercaptosuccinic acid (DMSA) (*4–8*). The precise mechanism of localization of ^{99m}Tc-MDP in amyloid has not been fully elucidated. However, expanded interstitial volume and impaired renal function are both likely to contribute. The intense uptake that is often seen, suggests that passive mechanisms alone do not fully explain the bone scintigraphic findings in amyloidosis. Some authors have advocated use of ^{99m}Tc-MDP imaging as a noninvasive method test for determining the extent and distribution of systemic amyloidosis (*9,10*).

Soft tissue accumulation of bone-seeking radiopharmaceuticals can occur in several diseases other than amyloidosis. A comprehensive gamut of causes of soft tissue localization of bone-seeking radiopharmaceuticals can be found elsewhere (*11–13*). The multitude of conditions that demonstrates soft tissue localization of bone-seeking radiopharmaceuticals cannot be explained by a single mechanism. Rather, there are several mechanisms, some of which have not been clearly defined, by which extraosseous, nongenitourinary, localization of bone-seeking radiopharmaceuticals may occur, (Table 1). In many diseases, more than one mechanism may be involved.

One of the most common mechanisms of soft tissue localization of bone-seeking radiopharmaceuticals is expanded interstitial volume. A dynamic equilibrium exists between osseous uptake of bone-seeking radiopharmaceuticals, intravascular volume and interstitial volume. As a consequence, any process that causes expanded interstitial volume will cause a relative increased passive localization of bone-seeking radiopharmaceuticals. The same mechanism will occur with any ^{99m}Tc chelate that has a relatively long residence time in blood. For example, Figure 4 demonstrates a female with breast carcinoma and bony metastases involving the left hemipelvis and right eighth rib. Diffuse increased soft tissue activity is also present over the entire abdomen which represents ^{99m}Tc-MDP activity within ascitic fluid. In addition, a more focal accumulation of activity is present in the right upper quadrant, related to liver metastasis. Hyperemia, which occurs with inflammation following trauma or sympathectomy, may also be as-

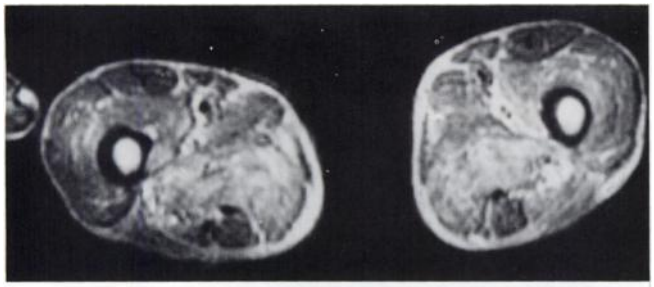

FIGURE 2. T2-weighted MRI demonstrating abnormally increased signal intensity within the proximal thigh musculature.

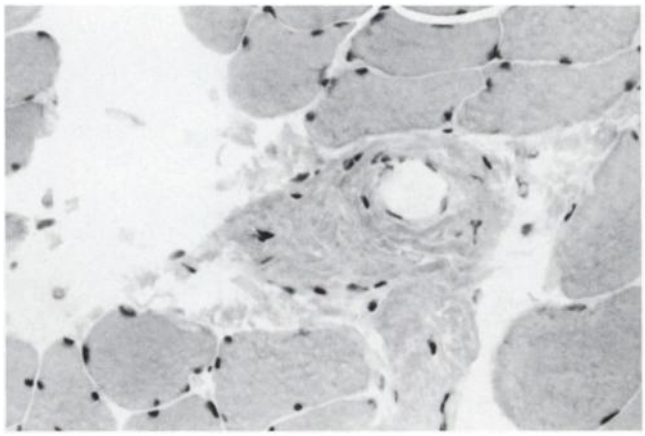

FIGURE 3. Hematoxylin and Eosin stained photomicrograph of left adductor muscle biopsy demonstrating infiltration of amyloid in blood vessel wall and adjacent perimysial connective tissue (100× magnification).

TABLE 1
Selected Mechanism for Soft Tissue Localization of Bone-Seeking Radiopharmaceuticals

Mechanism	Example
Expanded interstitial volume	Inflammation, infection, tumors, ascites, edema, effusions, renal failure, amyloidosis, rhabdomyolysis, post-trauma or postsympathectomy
Malignant new bone formation	Osteosarcoma or chondrosarcoma
Dystrophic calcification	Following ischemia or infarction, myositis ossificans, postradiotherapy, postchemotherapy, following trauma or surgery, vascular calcification, scleroderma or fibrodysplasia ossificans
Metastatic calcification	Hyperparathyroidism, renal failure or hypercalcemia
Transchelation with metals	Iron or calcium injections, iron overload states or hemochromatosis
Radiopharmaceutical factors	Misadministration, free pertechnetate, contamination or colloidization
Abnormal retention of activity in intravascular space	Renal failure, age, drug effects (diphosphonates, aluminum hydroxide, iron-containing compounds) or early imaging

sociated with increased interstitial volume and contribute to increased accumulation of the radiopharmaceutical in the affected area, particularly when blood concentrations of bone-seeking radiopharmaceuticals are high (early after injection or in older patients). Blood concentrations of bone-seeking agents may remain high in renal failure or when intravascular transchelation occurs following parenteral iron administration. If uptake in bone is competitively inhibited in patients who recently have received therapeutic diphosphonates used in treating osteoporosis or Paget's disease of bone, then high blood concentrations of bone-seeking agents can also occur.

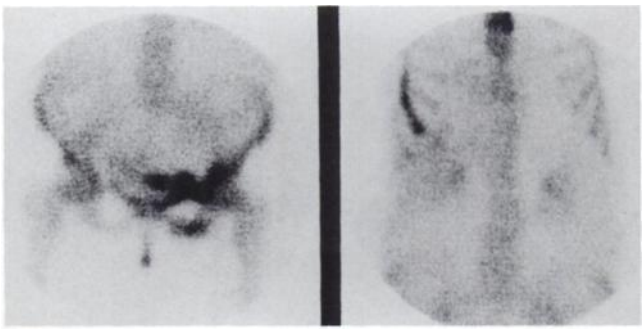

FIGURE 4. Bone scan performed 3 hr following the intravenous administration of ^{99m}Tc-MDP demonstrating accumulation of ^{99m}Tc-MDP within bony metastases involving the left hemipelvis and right eighth rib. In addition, diffuse increased accumulation of activity is present within ascitic fluid and a focal soft tissue accumulation of activity can also be identified in the right upper quadrant which represents soft tissue accumulation within liver metastases.

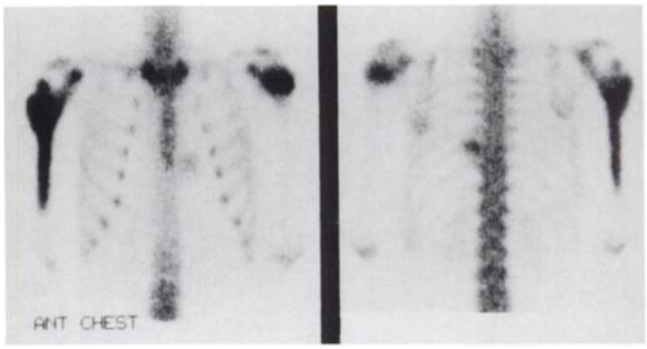

FIGURE 5. Technetium-99m-MDP bone scan from a young girl demonstrating abnormal accumulation of ^{99m}Tc-MDP within a primary osteogenic sarcoma of the right proximal humerus and left lung metastases.

Malignant new bone formation may cause rather intense and occasionally dramatic soft tissue localization of bone-seeking radiopharmaceuticals. Figure 5 demonstrates a young female with osteogenic sarcoma involving the right proximal humerus and malignant new bone formation within a left lung metastases. Figure 6 demonstrates extensive osseous and soft tissue localization of ^{99m}Tc-MDP in regions of metastatic ossification in a patient with a high grade osteogenic sarcoma.

Dystrophic calcification is the deposition of calcium salts occurring in degenerated or necrotic tissues. In degenerating or necrotic tissue, damage to cellular membranes causes an influx of ionized calcium. When the solubility product for calcium and phosphate is exceeded, intracellular precipitation of calcium as amorphous calcium phosphate and crystalline hydroxyapatite occurs. Table 1 lists common conditions in which soft tissue accumulation of bone-seeking radiopharmaceuticals occur by dystrophic calcification. Figure 7 demonstrates radiographically occult myositis ossificans occurring in a young male 8 wk following an ice hockey injury.

In contrast to dystrophic calcification, metastatic calcification is the deposition of calcium salts occurring in nonosseous, viable tissue in the presence of hypercalcemia. When hypercalcemia is severe or when serum protein concentrations are low, the solubility product for calcium and phosphate is exceeded and precipitation of calcium salts in the extracellular space occurs. Metastatic calcification usually involves joints (chrondrocalcinosis) and acid-secreting organs (stomach, kidney and lungs). Alteration in pH within these tissues seems to cause selective precipitation of calcium salts at these sites.

Transchelation of ^{99m}Tc-MDP may occur at injection sites where there is a high local tissue concentration of metals such as iron or calcium. This same mechanism may also be operative in organs with a high iron content occurring in iron overload states. In addition, after parenteral administration of iron, there may be transchelation with abnormally high blood concentrations of ^{99m}Tc no longer in the form of a phosphate. It should also be mentioned that the mechanism described above, especially transchelation

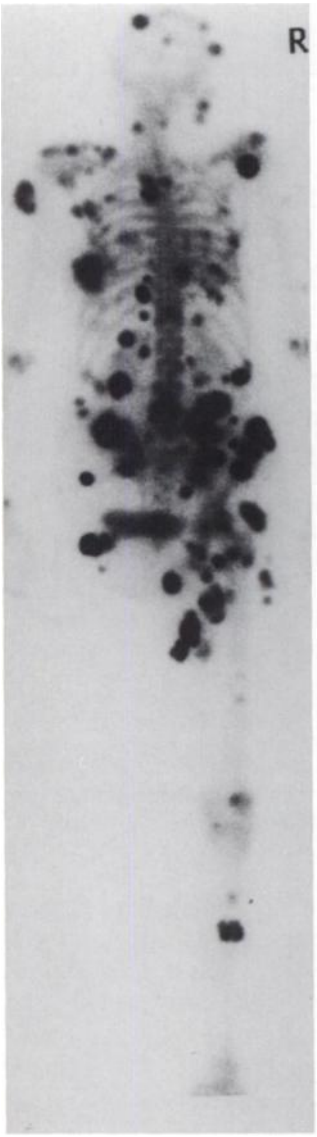

FIGURE 6. Posterior image from a 36-yr-old man with a high grade osteogenic sarcoma of the left proximal femur who underwent a left hemipelvectomy 1 yr ago. The bone scan demonstrates increased localization of activity within multiple osseous and soft tissue metastases.

and competitive inhibition, has been proposed as a plausible phenomenon rather than one proven to occur.

Other mechanisms of soft tissue localization of bone-seeking radiopharmaceuticals relate to abnormalities with the radiopharmaceutical including intra-arterial or interstitial injection, contamination, soft tissue accumulation of free pertechnetate and colloidization of ^{99m}Tc-MDP resulting in reticuloendothelial cell localization.

CONCLUSIONS

Amyloidosis is just one of a multitude of conditions that can cause soft tissue localization of bone-seeking radiopharmaceuticals. By understanding mechanisms by which

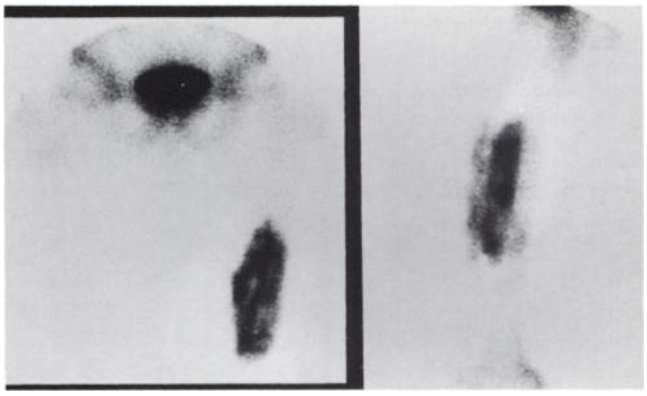

FIGURE 7. Technetium-99m-MDP bone scan performed 8 wk following a hockey injury demonstrating intense accumulation of ^{99m}Tc-MDP in a region of myositis ossificans.

soft tissue localization occurs, one can intuitively deduce pathological and nonpathological conditions in which it is likely to arise. Awareness of conditions that cause soft tissue localization of bone-seeking radiopharmaceuticals greatly enhances the diagnostic value of a bone scan and reduces the possibility of error in interpretation.

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