"COLD" BONE LESIONS: A NEWLY RECOGNIZED PHENOMENON OF BONE IMAGING

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"Cold" (photon-deficient) bone scan lesions are reported in seven patients with a variety of disease processes including metastatic disease, post-traumatic aseptic necrosis, and sickle cell-C crisis. Patients were studied with ^{99m}Tc-polyphosphate and/or ^{18}F scans and in two cases, ^{111}In-chloride bone marrow scans. Foci of decreased radioisotope activity were identified corresponding to sites of metastatic tumor and bone infarcts. Infarction may be a primary mechanism in the production of diminished radionuclide uptake in some of the cases. Consideration is given to a spectrum of abnormal bone-imaging manifestations (increased uptake, "normal" uptake, to photon-deficient) as a useful concept in the interpretation and understanding of bone scans.

It is common knowledge that bone scans performed with a variety of radiopharmaceuticals occasionally may be normal in the presence of metastatic disease to bone. Even so, only a few well-studied cases have been described and these have been associated generally with radiographically lytic lesions (*1–5,7*). It is the purpose of this report to document cases of focal diminished uptake (photon-deficient areas) of commonly used bone- and bone marrow-seeking radiopharmaceuticals in cases of skeletal damage due to malignancy or other lesions. In addition, a case is reported in which increased radiopharmaceutical uptake in a metastatic lesion subsequently reverted to a normal scan.

METHODS

Patients were injected intravenously with 15 mCi of ^{99m}Tc-polyphosphate or 4 mCi of ^{18}F and scanned 2–3 hr later. In the interim between injection and scanning, patients were hydrated and were asked to empty their bladders immediately prior to the scanning procedure. Technetium-99m-polyphosphate imaging was performed on either a scintillation camera (Searle Radiographics) with a high resolution, low-energy collimator, or on a dual-probe rectilinear scanner (Ohio-Nuclear Corp.) with a 3-in. focal depth low-energy collimator. Scanning with ^{18}F was done using a 5-in. focal depth high-energy collimator and the described rectilinear scanner. A 25% window was used for ^{99m}Tc-polyphosphate scanning and 200,000 counts were collected for each view. For the rectilinear scans, the scan speed was adjusted to obtain an information density of 1,000 counts/cm^2 with the upper probe over the sternum and the lower probe over the thoracic spine. Total-body images were obtained with 5:1 minification. The window settings were 10–20 keV centered on the 140-keV photopeak for ^{99m}Tc-polyphosphate and 100 keV for the 511-keV photopeak of ^{18}F.

In two instances, bone marrow scans were performed using 3 mCi of intravenously injected $^{111}InCl_3$. Forty-eight hours postinjection, rectilinear scanning was performed using the 173-keV photopeak, a 20-keV window, and an information density of 1,000 counts/cm^2, again using the sternum and thoracic spine for calibration.

RESULTS

Case 1. FW, a 40-year-old man, presented with a lung mass in October 1972. Adenocarcinoma of the lung was diagnosed and 3,500 rads were delivered to the primary lesion. During January 1973,

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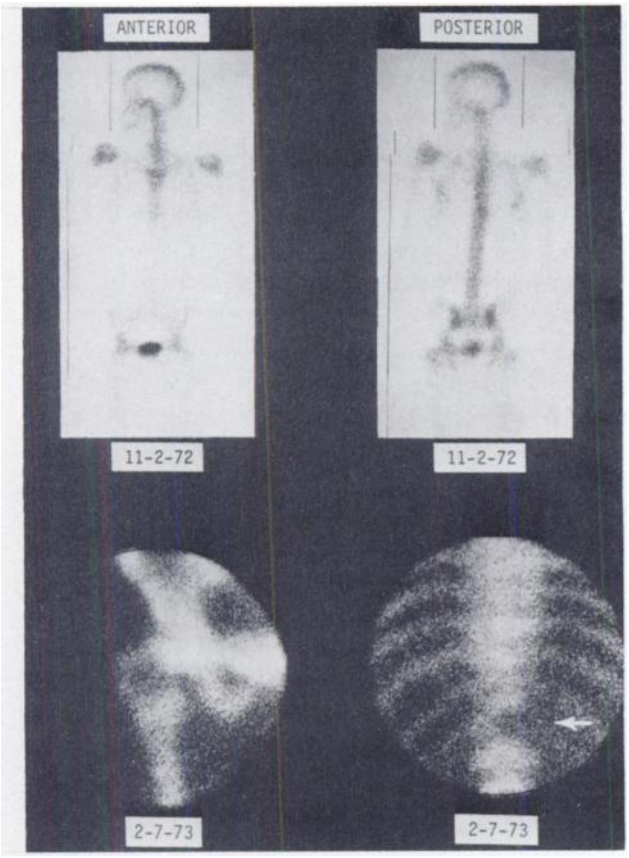

FIG. 1. Case 1. Technetium-99m-polyphosphate bone scan. Photon-deficient areas in right aspect of T_{12} vertebral body and right hip, Feb. 7, 1973. Contrast to normal study of Nov. 11, 1972. Radiograph showed lytic lesion of right T_{12} vertebral body with ballooning of pedicle. Adenocarcinoma of lung.

he was treated with a short course of chemotherapy (one dose each of cytoxan, 1.6 gm, and vincristine, 1.5 mg), because of malignant cells in his bone marrow. On January 27, 1973 he was readmitted with lethargy and back pain of several days' duration. The serum calcium was 11.9 mg%, phosphorus 2.8 mg%, and the alkaline phosphatase was 21.8 Bodansky units (normal 2–5). Parathormone assay was normal. Figure 1 shows the results of several studies on this patient. A ^{99m}Tc-polyphosphate bone scan (February 7, 1973) revealed a photon-deficient area in the right aspect of the T_{12} vertebral body and a large area of decreased uptake in the right hip. These findings were in contrast to a previously normal scan (November 2, 1972). Radiographs (February 10, 1973) revealed a lytic lesion of the right T_{12} vertebral body with involvement of the pedicle. Histopathologic correlation autopsy February 12, 1973) showed three distinct patterns of involvement of the T_{12} vertebral body. The first area was a portion of hyperplastic bone marrow containing spicules of cancellous bone. Here, there was a moderate degree of osteoblastic activity and frequent osteoid seams, indicative of bone remodeling. In a second area adjacent to the first, there was a region of poorly vascularized anaplastic tumor. Bone spicules in this area were viable but not particularly active. The third area consisted of frank necrosis with a background of ghostlike necrotic tumor as well as hyperplastic marrow. The bony spicules in this area displayed osteoid seams but little or no osteoblastic activity and there was a marked dropout of osteocytes within preformed bone, suggesting early bone necrosis.

Case 2. LR, a 55-year-old man, was first seen in June 1971. A diagnosis of epidermoid lung carcinoma was made and left pneumonectomy performed. In June 1972 cutaneous metastases were treated with a short course of 5-fluorouracil. He was readmitted on January 9, 1973 because of low back pain for several days. His serum calcium was 11.6 mg%, phosphorus 3.2 mg%, and the alkaline phosphatase was 11.1 Bodansky units. Radionuclide studies are shown in Fig. 2. An ^{18}F bone scan (January 10, 1973) revealed photon-deficient $T_{11/12}$ vertebral bodies. A similar scan was obtained 1 week later using $^{111}InCl_3$. The bone marrow scan was obtained 24 hr after 250 rads of external radiation to the lumbar region. Radiographs (January 13, 1973) showed lytic lesions of $T_{11/12}$ vertebrae. The patient died 5 weeks later, but a postmortem examination was not obtained.

Case 3. TR, a 54-year-old man, was found to have small-cell undifferentiated lung carcinoma early in 1972. Radiation therapy (5,000 rads) was given to the primary. About a week before hospital admission on December 7, 1972, he complained of right rib and lower lumbar pain. His serum calcium

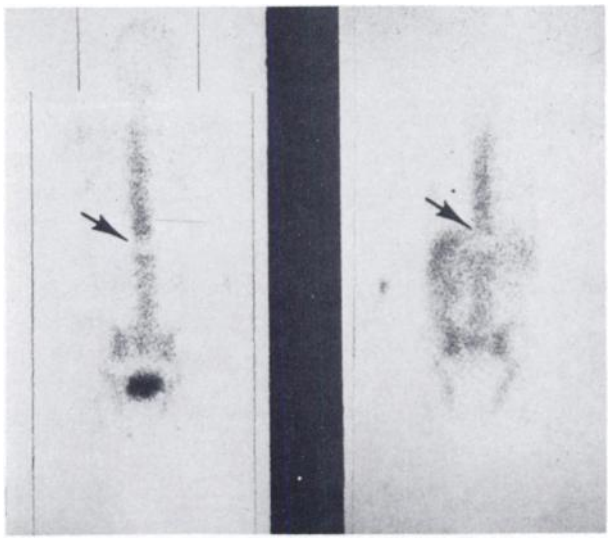

FIG. 2. Case 2. Fluoride-18 bone scan (left) on Jan. 10, 1973 and $^{111}InCl_3$ bone marrow scan (right) on Jan. 18, 1973 show photon-deficient area corresponding to $T_{11/12}$ vertebral bodies. Epidermoid lung carcinoma.

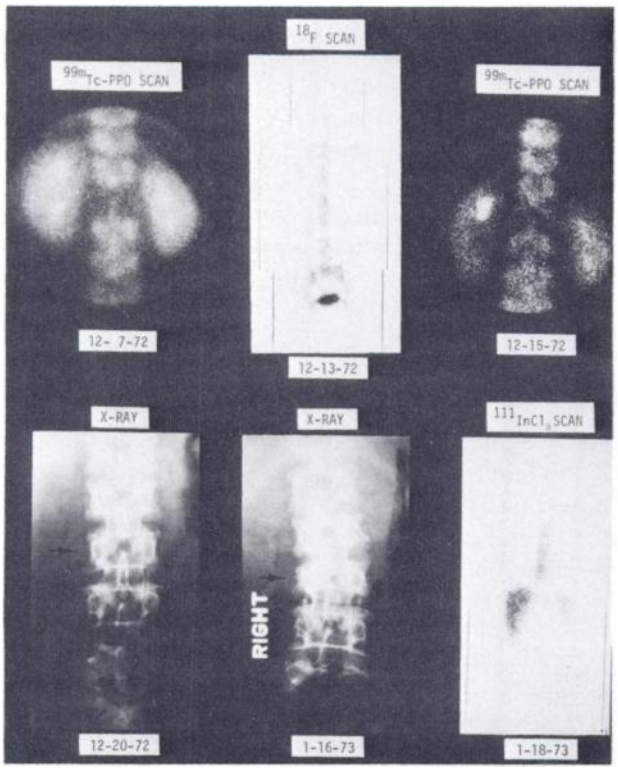

FIG. 3. Case 3. Technetium-99m-polyphosphate scans Dec. 7, 1972 and Dec. 15, 1972 reveal photon-deficient L_3 vertebral body. ^{18}F scan Dec. 13, 1972 shows similar results. Bone marrow scan Jan. 18, 1973 shows generally decreased marrow uptake below lower thoracic level. Radiographs Jan. 16, 1973 revealed compression fracture of L_3, not apparent on Dec. 20, 1972. Small-cell carcinoma of lung.

was 9 mg%, phosphorus 4.2 mg%, and the alkaline phosphatase was 14.8 Bodansky units. Technetium-99m-polyphosphate bone scanning on December 7, 1972 and December 15, 1972 revealed a photon-deficient L_3 vertebral body (Fig. 3) and increased uptake over several right anterior ribs. An ^{18}F bone scan on December 13, 1972 was identical to the ^{99m}Tc-polyphosphate scans. Bone marrow scanning (January 18, 1973) showed decreased vertebral marrow activity below the lower thoracic level. It should be noted that in this case, 350 rads of radiation therapy were administered to the lumbar spine just prior to the bone marrow scan; however, no radiation therapy or chemotherapy was given prior to the bone scans. Radiographs of the chest revealed extensive metastatic involvement of the right clavicle and many lower ribs with pathologic fractures of the ninth and tenth ribs. The third lumbar vertebra was normal radiographically on December 20, 1972 but a compression fracture of L_3 was discovered on repeat examination (January 16, 1973).

Case 4. CL, a 51-year-old man, was admitted on December 12, 1972 with a 2-week history of right subscapular pain. A mass was detected in the right lung and the sputum cytology was Class V. His serum calcium was 9 mg% and the alkaline phosphatase was 3.9 Bodansky units. Technetium-99m-polyphosphate bone scanning on December 15, 1972 showed a localized area of increased uptake in a right lower rib (Fig. 4). Radiographs of the ribs were normal. Subsequent ^{99m}Tc-polyphosphate scanning on December 26, 1972 and on January 2, 1973 showed a change from increased tracer to a "normal" degree of tracer uptake in the rib. An autopsy performed on January 5, 1973 revealed a large extraosseous mass of metastatic tumor in the region of the "hot" lesion. The tumor type was poorly differentiated adenocarcinoma. There were focal areas of tumor encroachment on the periosteum without definite cortical or intramedullary involvement. Separate from the area of tumor there was a disorganized array of necrotic bone with dystrophic calcification. No tumor was noted in this area. Visible bony architecture was not that of rib and is therefore construed as metaplastic bone in an area of injury resulting either from the proximity of tumor or trauma, or both.

Case 5. DJ, an 18-year-old girl with known sickle cell-C disease, was admitted on May 1, 1973, with complaints of right thigh pain which had extended to both legs and hips over several days. She had a past history of five painful bone crises but had been asymptomatic for the previous 10 months. On admission her hematocrit was 31 and the WBC 13,600 with a slight shift to the left. The sedimentation rate was 75. Urine was positive for occult blood. Treatment consisted of bed rest, intravenous hydration, and merperidine analgesia with almost complete resolution of symptoms in 5 days. Technetium-99m-polyphosphate bone scanning (May 10, 1973) revealed photon-deficient areas in the right hip with normal activity in the right femoral head and the left hip (Fig. 5). Radiographs were normal except for aseptic necrosis of the left hip, which was first recognized in October 1971.

Case 6. JC, a 60-year-old man, was admitted on July 19, 1973 with complaints of right hip pain of 6 months' duration and weight loss of 30 lb over

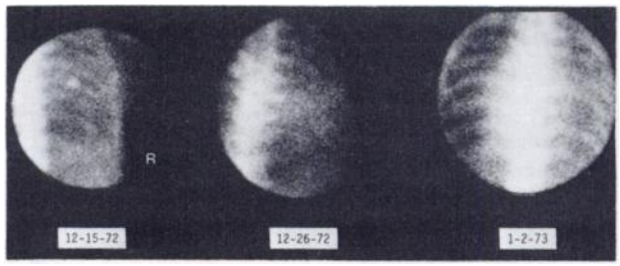

FIG. 4. Case 4. Technetium-99m-polyphosphate bone scans. Hot lesion in rib Dec. 15, 1972. Scans Dec. 26, 1972 and Jan. 2, 1973 fail to demonstrate "hot" lesion. Undifferentiated carcinoma.

the previous year. No other symptomatology was present. Admission radiographs revealed a lytic lesion of the right acetabulum. His serum calcium was 11.8 mg%, phosphorus 1.7 mg%, and the alkaline phosphatase was 9.7 Bodansky units. Technetium-99m-polyphosphate bone scanning (July 24, 1973) showed a photon-deficient area corresponding to the lytic x-ray lesion. Several days later a cystic mass was palpated in the deep gluteal muscles on the right. This was incised, revealing a 10 × 15 cavity containing necrotic material which extended to the right acetabulum. Microscopic examination revealed a squamous cell carcinoma. Sections of the involved bone were not obtained and a primary lesion has not been found.

Case 7. LB, a 46-year-old woman, sustained a traumatic right subcapital femoral fracture on February 5, 1972. The fracture was reduced and treated with a Deyerle pin apparatus, using a total of 10 pins. Following her operation, the patient experienced variable pain, increasing early in 1973. The Deyerle pins were removed during February 1973, and there was no evidence of infection. Between February and October of 1973, the patient complained of gradually increasing right hip pain, causing limited ambulation. Technetium-99m-polyphosphate scanning (October 10, 1973) revealed an area of decreased uptake involving the right femoral head (Fig. 6). Tomograms of the right hip revealed nonunion of the fracture and tracks from the pin sites. Because of persistent pain, a right total-hip arthroplasty was performed on November 15, 1973. Gross inspection of the femoral head revealed replacement of marrow by fatty tissue and many zones of gray white-appearing bone with focally hemorrhagic regions suggesting infarct. Microscopic examination revealed large areas of necrotic bone.

FIG. 6. Case 7. Technetium-99m-polyphosphate bone scan. Photon-deficient area involving right femoral head. Trauma.

DISCUSSION

In general, the identification of bone lesions by radionuclide imaging depends on the detection of a higher counting rate in the area of involved bone than in the adjacent tissues. That false-negative scans can occur is well known and has been reported in 2–5% of cases studied with ^{85}Sr (*2,3*). False-negative bone scans also have been reported using ^{18}F as the radiopharmaceutical (*4,5*). Roentgenograms in many of these cases showed osteolytic lesions. It should not be surprising, therefore, that areas of photon deficiency may be a manifestation of an abnormal bone scan; however, to our knowledge this phenomenon has not been previously reported.

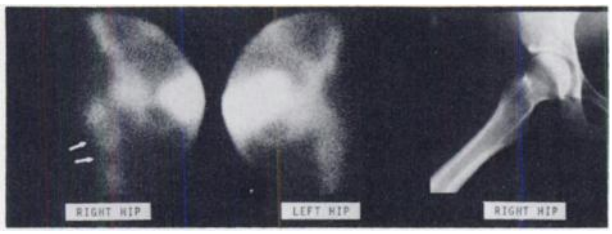

FIG. 5. Case 5. Technetium-99m-polyphosphate bone scan. Photon-deficient areas in right proximal femur; normal activity in left hip, site of long-standing aseptic necrosis. Radiography of right hip was normal. Sickle cell-C disease.

Although the various bone-imaging radiopharmaceuticals may have different mechanisms of association with bone tissue, in all cases some degree of vascular perfusion is a prerequisite for transport of the radionuclide to the bone structure. Regardless of what interrupts the transport (trauma, sickle cell sludging, infarction, tumor obstruction of vascular supply), the end result should be a decreased accumulation of radionuclide. In some of our cases, areas of photon-deficient bone may be explained by infarction alone. This was confirmed histologically in the case of aseptic necrosis secondary to trauma (Case 7), and is an acceptable explanation in the case of sickle cell-C crisis where sludging of abnormal cells may lead to bone infarcts (Case 5).

In other cases, the pathogenesis of the photon-deficient lesions is less clear. In the vertebral body, for example, there is an extensive blood supply (*6*) and production of a photon-deficient area by infarction of all of the feeder blood vessels seems unlikely. In those studies in which histopathologic correlation proved beyond doubt that a normal bone scan (neither increased nor decreased uptake) can occur

in the presence of invading tumor tissue, no evidence was found for true reactive bone formation at the site of the lesions (7). Presumably the amount of residual normal bone was sufficient to produce a false-negative (normal) scan. It is possible that some of our cases of photon-deficient scans may be the result of such total replacement or encroachment of the bony architecture by tumor, that the amount of viable residual bone is insufficient to yield a "normal" scan. The blood supply might remain intact but there would be too few viable cells to produce an image when scanned.

In every case in which bone imaging was performed using more than one radiopharmaceutical (Cases 2, 3), identical data were obtained. Marrow imaging likewise yielded comparable photon-deficient areas when this procedure was employed (Cases 2, 3). Of particular interest is the case in which a lesion reverted from "hot" to "normal" (Case 4). Pathologically, no definite area of rib was found to be involved with tumor but there was an area of metaplastic bone adjacent to the rib. This area of metaplastic bone could have caused the initial "hot" lesion, which returned to a "normal" degree of uptake following a disruption of its blood supply by encroaching tumor.

Major problems obviously exist in defining the number of false-negative bone scans that occur among the population studied. Even when the patient comes to autopsy it is rare that a total survey is made of all the bones that may be involved with tumor, thereby limiting the accuracy of the usual benchmark for abnormality used by medicine. In the patient who does not come to autopsy, we have only roentgenography or chemistry as a mechanism of detection of these lesions if they are not detected by the bone scan. The limitations of bone roentgenograms and serum chemistries in the detection of bone metastases are well known.

There are many unanswered questions regarding the pathology and physiology of photon-deficient areas. These foci of decreased radionuclide uptake may be thought of as representing one end of the spectrum of an abnormal bone scan which includes "hot," "normal," and "cold" (photon-deficient) areas. The recognition of this phenomenon should signal the need for a redefinition of the positive bone scan and a reassessment of the incidence of false-negative bone scans.

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