Combined Bone Scintigraphy and Indium-111 Leukocyte Scans in Neuropathic Foot Disease

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It is difficult to diagnose osteomyelitis in the presence of neurotrophic osteoarthropathy. We performed combined [^{99m}Tc]MDP bone scans and indium-111 (^{111}In) leukocyte studies on 35 patients who had radiographic evidence of neuropathic foot disease and clinically suspected osteomyelitis. The [^{111}In]leukocyte study determined if there was an infection and the bone scan provided the anatomic landmarks so that the infection could be localized to the bone or the adjacent soft tissue. Seventeen patients had osteomyelitis and all showed increased [^{111}In]leukocyte activity localized to the bone, giving a sensitivity of 100%. Among the 18 patients without osteomyelitis, eight had no accumulation of [^{111}In]leukocytes, seven had the [^{111}In]leukocyte activity correctly localized to the soft tissues, two had [^{111}In]leukocyte activity mistakenly attributed to the bone, and one had [^{111}In]leukocyte accumulation in a proven neuroma which was mistakenly attributed to bone. These three false-positive results for osteomyelitis reduced the specificity to 83%. Considering only the 27 patients with a positive [^{111}In]leukocyte study, the combined bone scan and [^{111}In]leukocyte study correctly localized the infection to the soft tissues or bone in 89%. Uninfected neurotrophic osteoarthropathy does not accumulate [^{111}In]leukocytes. We found the combined bone scan and [^{111}In] leukocyte study useful for the detection and localization of infection to soft tissue or bone in patients with neuropathic foot disease.

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It is difficult to detect osteomyelitis superimposed on neurotrophic osteoarthropathy using routine radiographic studies (*1*). Since indium-111 (^{111}In) leukocytes generally do not accumulate in areas of increased bone turnover, they would not be expected to accumulate in neuropathic bone (*2*). Thus, focal accumulation of [^{111}In]leukocytes should indicate infection. Unfortunately, Maurer et al. found it difficult to distinguish osteomyelitis from adjacent soft-tissue infection (*3*). This differentiation is important since osteomyelitis requires more aggressive therapy than cellulitis (*4*).

In this study we combined the bone scan with the [^{111}In]leukocyte study to overcome the low spatial resolution of the [^{111}In]leukocyte study, while retaining its high sensitivity and specificity. The bone scan provided the anatomic landmarks for the correct localization of the [^{111}In]leukocyte activity. The goal was to detect and to accurately localize infection to bone and/or to the adjacent soft tissues of the feet.

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MATERIALS AND METHODS

Patient Population

We studied 35 patients with suspected osteomyelitis and radiographic changes consistent with neuropathic foot disease. There were 26 males, and nine females, aged 19 to 74 with a mean of 53 yr. The patients had the following diseases: 26 had diabetes, three had trauma, three had meningomyeloceles, two had alcohol induced peripheral neuropathy and one had "Charcot-Marie Tooth" disease. The "correct diagnosis" was established by histology in 15 cases and by discharge diagnosis and follow-up in 20 cases.

Protocol for Combined Bone Scan and Indium-111 Leukocyte Study

1. After obtaining informed consent, the patient's blood was drawn for separation and labeling, as described previously (*2,5,6*).
2. Flow and blood-pool images of the three-phase bone scan were then obtained using technetium-99m methylene diphosphonate ([^{99m}Tc]MDP),
3. The [^{111}In]leukocytes were injected when the labeling was completed.
4. Three hours following [^{111}In]leukocyte injection, using a medium-energy collimator, the [^{99m}Tc]MDP bone image was obtained at 140 keV (20% window). Then, without moving

the patient, the camera window was changed to 247 keV (20% window) and the ^{111}In image was obtained. This process was then repeated in an orthogonal projection.

5. The orthogonal bone and ^{111}In images were repeated the following day with ^{111}In windows of 10% for the 173 keV peak and 20% for the 247 keV peak.

Image Analysis

The [^{99m}Tc]MDP bone and [^{111}In]leukocyte images were obtained on separate sheets of transparent film. Since they superimpose perfectly, it was readily apparent whether the [^{111}In]leukocyte activity was within the bone or outside of the bone. Unfortunately, this technique can not be illustrated; thus, it was necessary to place arrows around the [^{111}In] leukocyte activity in Figures 2 and 3.

A second approach would be to store the images in a computer and display the [^{111}In]leukocyte image in one color and the [^{99m}Tc]MDP image in another. Again, superimposition of the [^{111}In]leukocyte and [^{99m}Tc]MDP activity would be readily apparent.

RESULTS

All 35 patients selected for this study had radiographic changes consistent with neuropathic bone disease and increased accumulation of [^{99m}Tc]MDP on all three phases of the three-phase bone scan (Fig. 1).

Seventeen patients had osteomyelitis. All of these patients had the [^{111}In]leukocyte activity correctly localized to the bone (Fig. 3). This gave a sensitivity of 100%.

Eighteen patients had a diagnosis other than osteomyelitis. In 15 there was either no accumulation of [^{111}In]leukocyte activity (eight patients), or the [^{111}In] leukocyte activity was correctly localized to the soft tissues (seven patients) (Fig. 2). These 15 true negatives for osteomyelitis gave a specificity of 83%. There were three false-positive results. In two cases of clinically diagnosed cellulitis, and one surgically proven neuroma, the [^{111}In]leukocyte activity was mistakenly attributed to the bone.

If one considers only the 27 positive [^{111}In]leukocyte studies, the combined bone scan and [^{111}In]leukocyte study correctly localized the infection to soft tissue or to bone in 89%.

DISCUSSION

For neurotrophic osteoarthropathy to occur, there must be a change in the sensory nerves and subsequent trauma to the affected area (*7*). At present the most common etiology is diabetes mellitus, but other causes such as syphilis, peripheral nerve damage, or spinal cord injury by trauma, birth defect, tumor, or infection, have been reported (*7*).

Osteomyelitis can be difficult to evaluate using the conventional methods when there are superimposed bony changes from the neurotrophic osteoarthropathy (*1*). Radiographically, neuropathic bone has mixed sclerotic and lytic changes (*8*) which make differentiation from osteomyelitis difficult (*9*). The three phase bone scan increased the specificity for osteomyelitis (*10,11*).

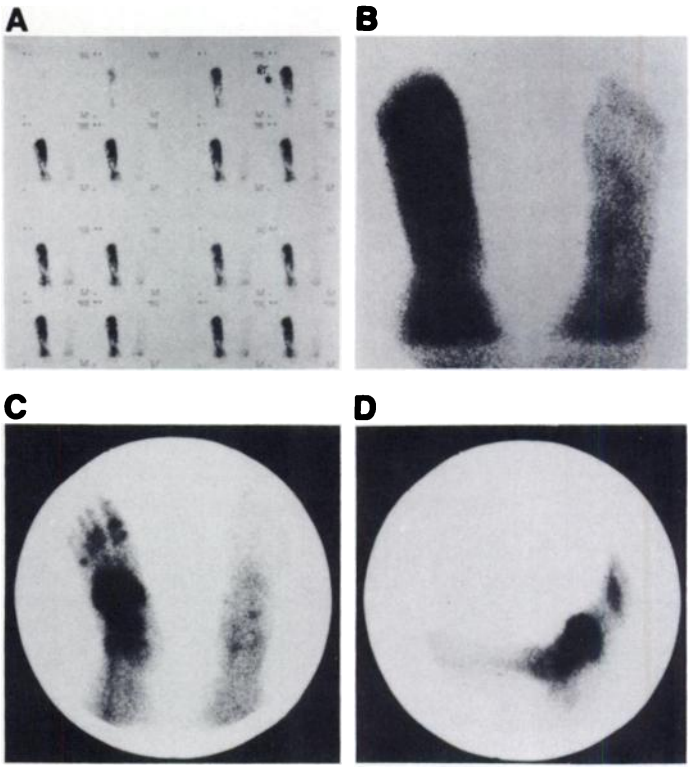

FIGURE 1
Sixty-one-year-old female diabetic with cellulitis and possible osteomyelitis. A: Flow phase, B: Blood-pool phase, C: Anterior and D: Right lateral delayed images. The increased activity in all images would be consistent with cellulitis in a patient with neuropathic osteopathy, but is osteomyelitis present as well? Figure 2 is the same patient.

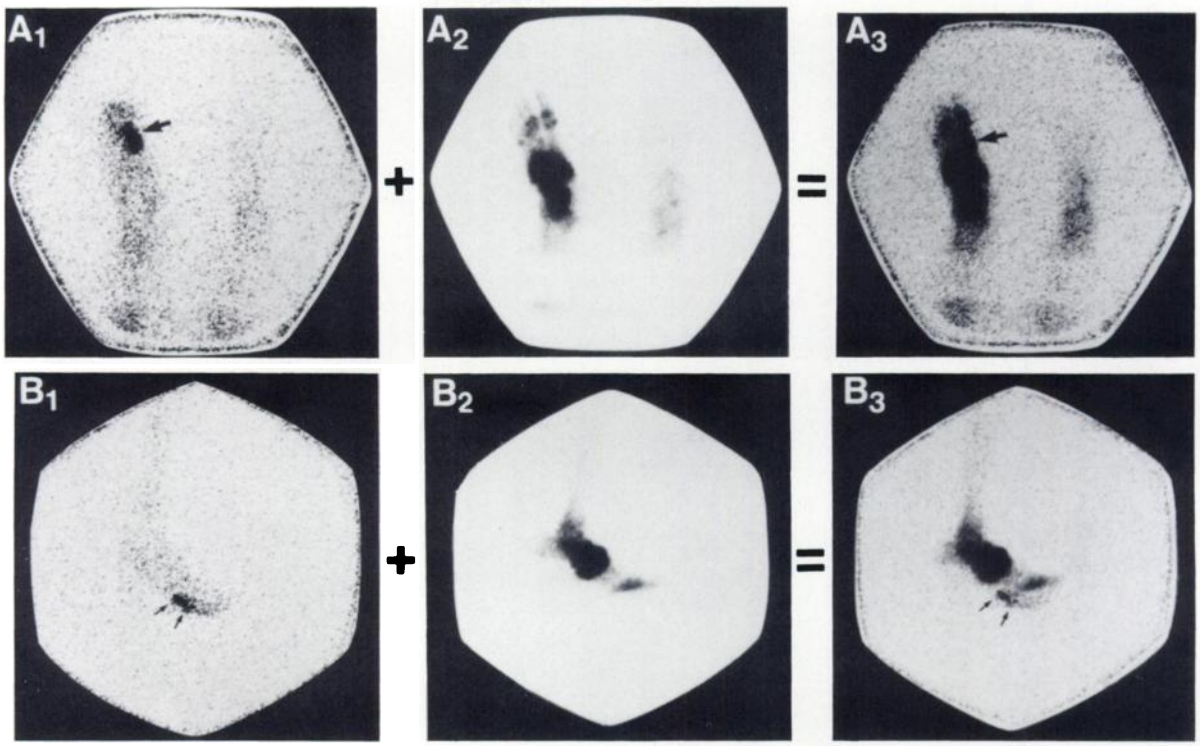

FIGURE 2
Same patient as illustrated in Figure 1. A1 and B1 show the plantar and right lateral 24-hr [^{111}In]leukocyte images, respectively. A2 and B2 are the plantar and right lateral bone images, respectively, obtained at the same time as A1 and B1. A3 is A1 superimposed on A2, and B3 is B1 superimposed on B2. The focal [^{111}In]leukocyte accumulation is clearly located in the soft tissues inferior to the bone. At surgery the patient had a soft-tissue abscess.

Unfortunately, the three-phase bone scan loses specificity when the suspected osteomyelitis is superimposed upon neurotrophic osteoarthropathy or other conditions which cause increased bone turnover (*12–15*). This is well illustrated by Figure 1 which shows intense uptake in all three phases, making the differentiation of uncomplicated neuropathic changes from neuropathic changes with superimposed osteomyelitis difficult, if not impossible.

Gallium-67 (^{67}Ga) citrate is known to localize in areas of infection. Since ^{67}Ga was proposed as a bone scanning agent (*16*), ^{67}Ga shows increased uptake in regions of increased bone turnover, such as neuropathic changes (*17,18*). Using ^{67}Ga it is difficult to get both high sensitivity and high specificity when trying to evaluate osteomyelitis superimposed upon diseases which cause increased bone turnover (*2*).

The [^{111}In]leukocyte study has also been proposed for the evaluation of osteomyelitis superimposed upon neuropathic changes or increased bone turnover (*2,3*). While sensitive and specific, the low spatial resolution makes the differentiation of soft tissue versus bone infection difficult (*3*). We, therefore, used the high spatial resolution of the bone scan to provide anatomic landmarks which would better localize the [^{111}In]leukocyte activity.

When performing simultaneous studies with two different isotopes, good technique is essential. For example, Fernandez-Ulloa et al. indicated that a 10% window at the 173 keV ^{111}In peak would effectively exclude the 140 keV ^{99m}Tc peak (*19*). We have found that if the ^{99m}Tc activity was extremely intense, by "summation peak" phenomenon, it was seen even in the 247-keV ^{111}In window. For example, we frequently saw ^{99m}Tc activity in the bladder contribute to the ^{111}In image at 3-4 hr. We did not use the 173 keV ^{111}In peak for the early images. When the delayed images were obtained, most of the [^{99m}Tc]MDP had decayed or been excreted. Thus, in agreement with Fernandez-Ulloa et al., we experienced no problems by including a 10% window at the 173 keV ^{111}In peak (*19*). Including the 173 keV peak enabled us to acquire enough counts for an acceptable image in ~20 min of imaging time.

The eight patients with no [^{111}In]leukocyte accumulation presented another interesting observation. Seven of these patients had diabetes and one had massive trauma; all had ulcers. Mal performans ulcers occur beneath bony prominences from the pressures of normal walking on a foot without normal pain sensation (*20*). With poor hygiene these ulcers can subsequently become infected; however, with good hygiene the ulcers can heal without infection or other complications (*20*).

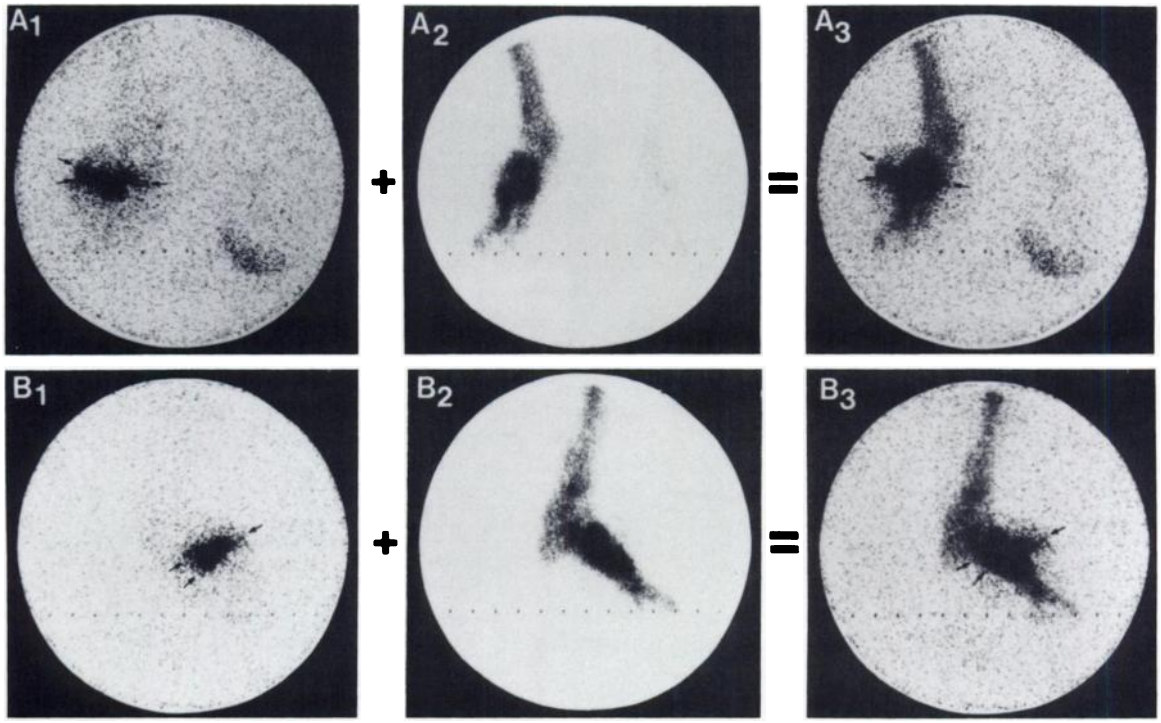

FIGURE 3
Nineteen-year-old male with meningomyelocele and a large ulcer and soft-tissue swelling on the dorsum of his right foot. A1 and B1 are the dorsal and right lateral 24-hr [^{111}In]leukocyte images, respectively. A2 and B2 are the dorsal and right lateral bone images respectively. A3 is A1 superimposed on A2 and B3 is B1 superimposed on B2. (The activity on the sole of the left foot is an artifact caused by rubbing the dorsum of the right foot. This activity was not present on the 4-hr images and was readily removed by washing.) On the orthogonal projections the ^{111}In activity lies both within and outside of the bone activity. This would be read as both osteomyelitis and cellulitis. The patient subsequently had an amputation. The pathology report indicated both chronic osteomyelitis and soft-tissue infection.

It may be that while ulcers were present, they may not have been infected at the time the ^{111}In leukocyte study was performed in these eight patients.

As expected, neuropathic bone did not accumulate [^{111}In]leukocytes in the absence of infection. Using the orthogonal projections, we were able to correctly localize the ^{111}In uptake to soft tissue or bone in 89% of the cases (Figs. 2 and 3). In addition, we were able to obtain a sensitivity of 100% and a specificity of 83% for osteomyelitis. These results are better than we generally obtain when studying osteomyelitis with [^{111}In]leukocyte (*2,5,6*). There are at least two factors which may contribute to the improved results in the feet. First, the bones make up a large proportion of the total tissue imaged. Other areas have a larger contribution from the soft tissues which may contribute to the background. Second, the appendicular skeleton in the adult contains no active bone marrow. Since active bone marrow also accumulates [^{111}In]leukocytes, diagnosis of osteomyelitis in the axial skeleton has decreased sensitivity (*21*).

In conclusion, we found the combined bone scan and [^{111}In]leukocyte study to be sensitive, specific, and capable of localizing the infection to the soft tissue or to bone in patients with neuropathic changes in the feet.

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