

Marrow Versus Infection in the Charcot Joint: Indium-111 Leukocyte and Technetium-99m Sulfur Colloid Scintigraphy

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This study evaluated the role of combined leukocyte/marrow scintigraphy in the assessment of the neuropathic or Charcot joint. **Methods:** Seventeen patients with ^{111}In -labeled leukocyte accumulation in 20 radiographically confirmed Charcot joints underwent $^{99\text{m}}\text{Tc}$ -sulfur colloid marrow scintigraphy. Studies demonstrating labeled leukocyte accumulation without corresponding activity on marrow images were classified as positive for osteomyelitis. Six of the patients also underwent three-phase bone scintigraphy. Bone scans were interpreted as positive for osteomyelitis when focal hyperperfusion, focal hyperemia and focal bony uptake on delayed images were present. Bone images were also interpreted together with labeled leukocyte images using two different criteria for a positive study. One criterion was the presence of labeled leukocyte activity in a region demonstrating abnormal activity on the bone scan, which was more intense than adjacent marrow activity or marrow activity in the corresponding region of the contralateral foot. The second criterion was either a spatially incongruent distribution of the two tracers or hyperintense activity on the leukocyte study, as compared to the bone scan. **Results:** Leukocyte/marrow studies were positive for osteomyelitis in 4 of the 20 neuropathic joints. Osteomyelitis was present in three of the four joints, whereas in the fourth, infection was confined to overlying soft tissues. None of the 16 neuropathic joints with negative leukocyte/marrow scans were infected. In one patient who underwent below-the-knee amputation, histological analysis confirmed the presence of hematopoietically active marrow corresponding to areas of congruent activity on the leukocyte and marrow images. Three-phase bone scintigraphy was positive in all six neuropathic joints studied; osteomyelitis was present in two of them. Using the first criterion, leukocyte/bone imaging was also positive in all six. Using the second criterion, leukocyte/bone imaging was positive in the two infected neuropathic joints, as well as in three uninfected ones. Leukocyte/marrow scintigraphy was positive in both infected joints and negative in the four without infection. **Conclusion:** Labeled leukocyte accumulation in the uninfected Charcot joint does occur and is related, at least in part, to hematopoietically active marrow. Leukocyte/marrow scintigraphy is a reliable way to differentiate between marrow and infection as the cause of labeled leukocyte accumulation in the neuropathic joint and, in this series, was superior to both three-phase bone scintigraphy and combined leukocyte/bone scintigraphy.

Key Words: Charcot joint; osteomyelitis; labeled leukocyte imaging; marrow scintigraphy

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Neuropathy that is secondary to a variety of causes may be complicated by an arthropathy, which can be very severe. First described by Charcot in the 19th century, the neuropathic or Charcot joint has been associated with a variety of diseases, including tabes dorsalis, syringomyelia, leprosy, amyloidosis

and hereditary sensory neuropathy (1). The most common cause of the neuropathic joint today, however, is diabetes mellitus (2). The clinical presentation and radiographic changes that accompany this entity make the differentiation between the neuropathic joint, with and without osteomyelitis, a diagnostic challenge.

The considerable new bone formation that is part of this entity limits the use of the sensitive, but nonspecific, radionuclide bone scan (3-6). Although labeled leukocytes do not usually accumulate in areas of increased bone mineral turnover in the absence of infection, false-positive results in the neuropathic joint have been reported (6,7). Because marrow scintigraphy enhances the specificity of labeled leukocyte imaging in complicating osteomyelitis (8-10), we have begun using combined leukocyte/marrow scintigraphy in an attempt to differentiate the infected from the uninfected Charcot joint. The data that follow represent a retrospective review of our experience to date with this technique.

MATERIALS AND METHODS

Patient Population

Seventeen patients (13 women, 4 men; age range 42-83 yr; mean age 63 yr) with labeled leukocyte accumulation in the hindfoot (proximal tarsal bones) or midfoot (distal tarsal/proximal metatarsal bones) who underwent complimentary marrow scintigraphy are included in this retrospective review. Sixteen of the patients suffered from diabetes mellitus, 11 of whom were insulin-dependent. The duration of their disease ranged from 2 to 30 yr. The remaining patient had CREST syndrome, a congenital illness characterized by calcinosis, Raynaud's phenomenon, esophageal dysmotility, syndactyly and telangiectasia (11). The indications for labeled leukocyte imaging were suspected osteomyelitis of the hindfoot or midfoot ($n = 8$), the forefoot ($n = 6$) and tibia ($n = 1$) and fever of unknown origin ($n = 2$).

Radionuclide Studies

Imaging Parameters. Patients underwent labeled leukocyte imaging approximately 24 hr after injection of 18.5 MBq (500 μCi) of ^{111}In -labeled mixed autologous leukocytes prepared according to the method of Thakur et al. (12). Imaging was performed on a large-field-of-view gamma camera, equipped with a medium energy, general-purpose, parallel-hole collimator. Energy discrimination was accomplished by using a 15% window centered around the 174-keV photopeak of ^{111}In and a 20% window centered around the 247-keV photopeak of ^{111}In . Dorsal, plantar, lateral and medial views of the ankles and feet were routinely acquired for 12 min per view on a $128 \times 128 \times 16$ matrix.

After completion of the labeled leukocyte study, patients were injected with ~ 370 MBq (10 mCi) of $^{99\text{m}}\text{Tc}$ -sulfur colloid, with imaging performed approximately 1 hr later. For single-isotope ($^{99\text{m}}\text{Tc}$) acquisition ($n = 6$), a large-field-of-view gamma camera, equipped with a low-energy, high-resolution, parallel-hole collima-

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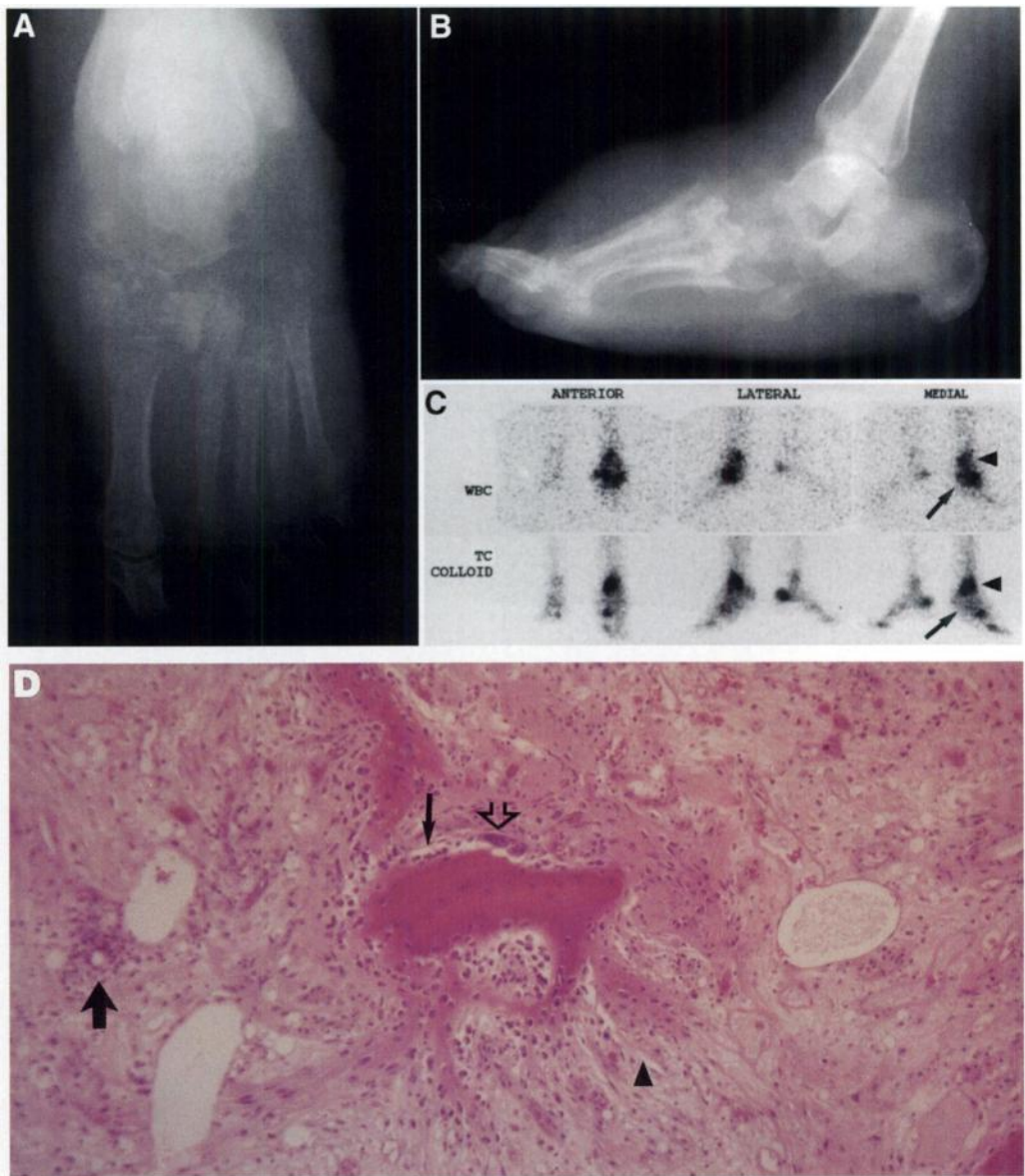


FIGURE 1. (A and B) Anterior-posterior and lateral radiographs of the left foot of a 54-yr-old woman, who had had insulin-dependent diabetes mellitus for 20 yr, demonstrate soft tissue swelling with extensive osteolysis and disorganization of several tarsal bones extending into and involving the second to fifth metatarsal bones consistent with a Charcot joint. The presence or absence of superimposed osteomyelitis cannot be assessed. (C) Labeled leukocyte and marrow images are congruent in the distal left tibia and talus, consistent with marrow (arrowheads). There is uptake of labeled leukocytes without corresponding uptake of sulfur colloid (incongruent images) in the distal tarsal and proximal metatarsal bones, consistent with osteomyelitis (arrows). Note congruent uptake of both tracers in the calcaneus and head of the first metatarsal on the right, indicative of hematopoietically active marrow at these sites. (D) Photomicrograph of a section through the hindfoot of this patient demonstrates evidence of osteomyelitis with new bone formation (arrowhead), osteoclasts (open arrow) and osteoblasts (thin arrow). Hematopoietically active marrow, consisting primarily of normoblasts (thick arrow), is also present.

tor, was used. Six-minute images of the region(s) of interest were acquired on a $128 \times 128 \times 16$ matrix using a 10% window centered around the 140-keV photopeak of ^{99m}Tc .

When simultaneous dual-isotope acquisition was performed ($n = 11$), a medium-energy, general-purpose, parallel-hole collimator was used, and energy discrimination was accomplished by using a 10% window centered around the 140-keV photopeak of ^{99m}Tc , a 5% window centered around the 174-keV photopeak of ^{111}In and a 10% window centered around the 247-keV photopeak of ^{111}In . Dual-isotope images were acquired on a $128 \times 128 \times 16$ matrix for 12 min per image. The 174-keV and 247-keV photopeak (leukocyte) images were summed and normalized to the 140-keV photopeak (sulfur colloid) images. The selection of sequential versus simultaneous acquisition was governed by equipment availability.

Six of the 17 patients underwent three-phase bone scintigraphy using ~ 740 MBq (20 mCi) of ^{99m}Tc -hydroxymethylene diphosphonate, a high-resolution, parallel-hole collimator and a 20% window centered around the 140-keV photopeak of ^{99m}Tc . At least 48 hr elapsed between the leukocyte/marrow study and bone scintigraphy in all six cases.

Image Interpretation. All images were interpreted as a consensus reading by two nuclear physicians blinded to the final diagnoses. Combined leukocyte/marrow studies were classified as positive for

osteomyelitis when activity was present on the leukocyte images without corresponding activity on the marrow images (incongruent study). When activity was present and spatially congruent on both leukocyte and marrow images, the combined studies were classified as negative for osteomyelitis.

Focal hyperperfusion, focal hyperemia and focal bony uptake on three-phase bone scintigraphy were classified as positive for osteomyelitis. When bone and leukocyte images were interpreted together, two different criteria for a positive study were used. A study in which leukocyte activity corresponded to abnormal activity on the bone scan and was more intense than adjacent marrow activity or activity in the contralateral foot was one criterion for a positive study (6). The second criterion for a positive study was an incongruent distribution of labeled leukocytes and bone tracer either spatially or in terms of intensity, i.e., labeled leukocyte activity, more intense than bone tracer activity (9).

RESULTS

Twenty sites of labeled leukocyte accumulation involving the hind- or midfoot were identified among the 17 patients. In 14 patients, the activity was confined to one foot, and in three patients, it was bilateral. Radiographic changes consistent with a neuropathic joint were present in all 20 sites (Fig. 1, A and B). Four of the neuropathic joints demonstrated an incongruent

distribution of labeled leukocytes and sulfur colloid and were interpreted as positive for osteomyelitis (Fig. 1C). There was histopathological confirmation available for three: in two, osteomyelitis was present, whereas in one, the infection was limited to soft tissues. In the fourth patient, the diagnosis of osteomyelitis was made clinically, and the patient was treated accordingly. One patient with osteomyelitis underwent below-the-knee amputation. Histopathological analysis demonstrated areas of osteomyelitis, as well as hematopoietically active marrow (Fig. 1D).

Leukocyte/marrow images were congruent or negative for osteomyelitis in 16 neuropathic joints (Fig. 2). In 12 of the 16, the leukocyte uptake was an incidental finding unrelated to the indication for the procedure. In the other four cases, patients responded to treatment of the Charcot joint itself and/or a short course of oral antibiotics, and osteomyelitis was, clinically, deemed unlikely. The overall accuracy of the combined technique was 95% (19/20).

Of the six Charcot joints studied with bone, labeled leukocyte and marrow imaging, osteomyelitis was present in two. Three-phase bone scintigraphy was positive in all six (100% sensitivity and 0% specificity) (Fig. 3, A and B). When interpreted according to the first criterion, bone/leukocyte imaging was also positive in all six neuropathic joints. When interpreted according to the second criterion, the combined study was positive in both infected joints, as well as in three of four uninfected neuropathic joints. Leukocyte/marrow scintigraphy was positive in both cases of osteomyelitis and negative in the other four (Fig. 3C) (Table 1).

DISCUSSION

Neuropathy, secondary to various causes, can be complicated by an arthropathy, resulting in the so-called neuropathic or Charcot joint. The neuropathic joint typically presents with swelling (often massive), crepitus (due to extensive destruction of bone and cartilage), instability, palpable loose bodies and large osteophytes. Pain may be present, but it is typically less than what would be expected from the appearance of the joint. Synovial effusions are generally noninflammatory or hemorrhagic, and the predominant cell type present in the effusion is mononuclear (1). About 5% of patients with diabetes mellitus and neuropathy develop a neuropathic joint, most often involving the tarsal or tarsometatarsal joints (1). The clinical presentation and radiographic changes that accompany this entity make the diagnosis of osteomyelitis superimposed on the Charcot joint a diagnostic challenge. Although useful for musculoskeletal infection in general, the value of magnetic resonance imaging in this entity is uncertain. The little data that are available are inconsistent. One group of investigators reported 100% sensitivity, with 0% specificity (6). Another group reported that an MRI accurately excluded osteomyelitis superimposed on neuropathic joints (100% specificity) (13). There were, however, no infected neuropathic joints in this series.

Although it is exquisitely sensitive, three-phase bone scintigraphy cannot reliably distinguish between osteomyelitis and the neuropathic joint because extensive bony remodeling is present in both conditions (3–6). All six Charcot joints in our population had three-phase bone scintigraphs compatible with osteomyelitis, yet only two of the joints were infected (100% sensitivity and 0% specificity).

Initially reported to be useful for discriminating between the neuropathic joint and osteomyelitis, recent reports indicate that uptake of labeled leukocytes in the uninfected Charcot joint

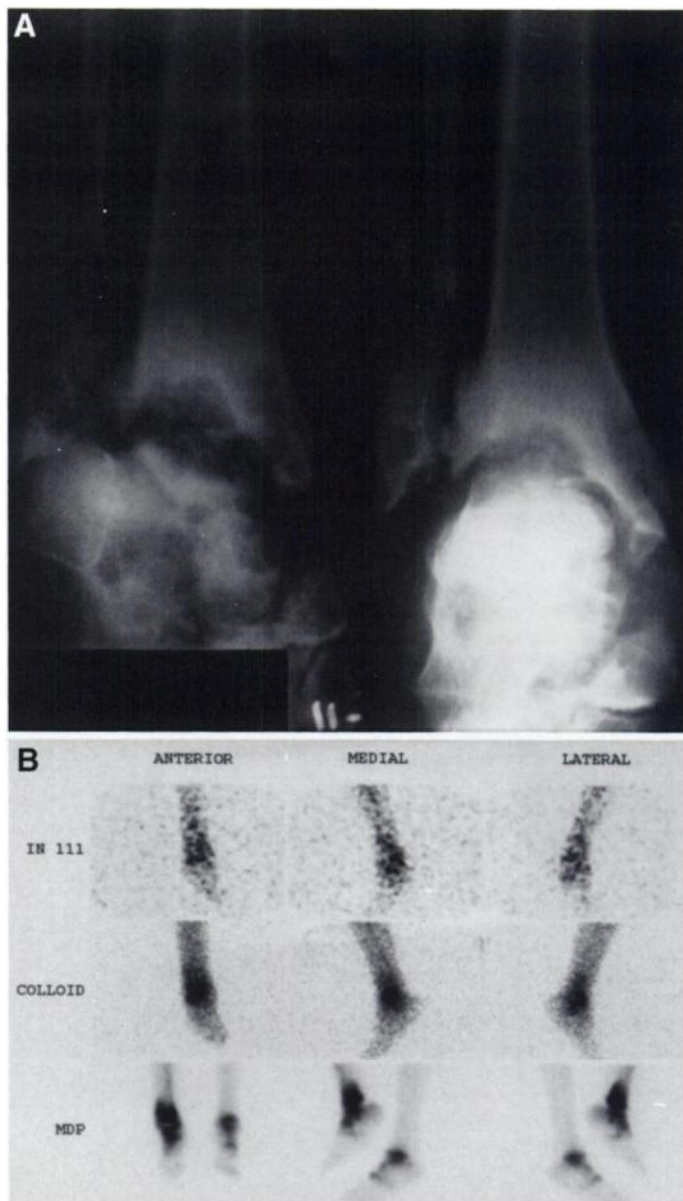


FIGURE 2. (A) A 59-yr-old woman, who had had insulin-dependent diabetes for 30 yr, presented with pain and swelling of the right ankle and foot. Radiographs reveal bony destruction, new bone formation and tarsal dislocations consistent with a Charcot joint. As in the first case, it is not possible to determine whether or not osteomyelitis is also present. (B) Labeled leukocyte, sulfur colloid and bone images. The distribution of labeled leukocytes and sulfur colloid is congruent, confirming that the leukocyte activity in this joint is due to marrow, not infection. The distribution of activity on labeled leukocyte and bone images is spatially congruent. The intensity of uptake on the leukocyte images is greater than adjacent marrow activity but less than that on the bone scan. Using the first criterion, the combined study is positive for osteomyelitis; using the second criterion, the combined study is negative for osteomyelitis.

does occur. In one series, 5 of 10 uninfected neuropathic joints demonstrated this phenomenon (6,7).

Speculation about the causes of these false-positive labeled leukocyte studies has centered on the inflammation, fractures and reparative processes that are associated with the neuropathic joint (6,7). The synovial effusions present in this entity are usually noninflammatory or hemorrhagic; moreover, the predominant cell type present in the effusion is mononuclear (1). The inflammatory response that accompanies fracture is polymorphonuclear only in its earliest phase. The poor sensitivity of labeled leukocyte imaging for detecting inflammatory and infectious conditions, in which the cellular response is other

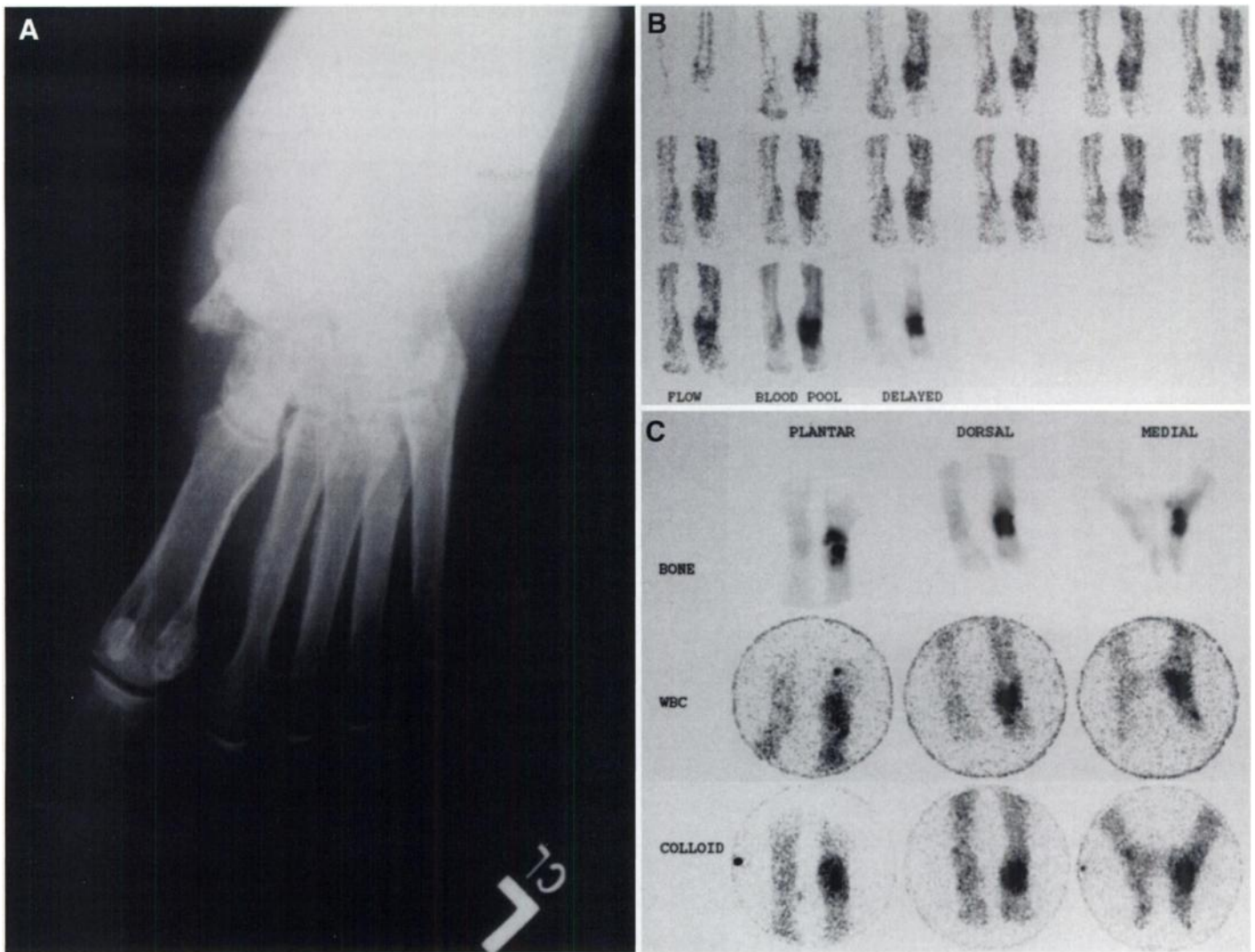


FIGURE 3. (A) Left foot radiograph of a 54-yr-old woman, with a 10-yr history of insulin-dependent diabetes and a 3-wk history of left foot pain, demonstrates soft tissue swelling and multiple fracture/dislocations of the midfoot, consistent with a neuropathic joint. (B) Three-phase bone scan is consistent with osteomyelitis in this region. (C) Combined bone/leukocyte study is positive for osteomyelitis, regardless of the criterion used. The distribution of activity in the Charcot joint is congruent on the leukocyte/marrow study, and hence, this study is negative for osteomyelitis. Leukocyte/marrow imaging is positive for osteomyelitis in the head of the left second metatarsal, which was the actual area of concern in this patient. Both the bone scan and radiograph are (falsely) negative at this site.

than polymorphonuclear, is well-documented, and it is unlikely, therefore, that labeled leukocyte uptake in the uninfected Charcot joint can be attributed solely to inflammation (14,15).

Our data indicate that such uptake in the absence of infection reflects, at least in part, marrow activity. Exactly why there should be hematopoietically active marrow in such an unusual location is uncertain. One possibility is that the development of hematopoietically active marrow is part of the arthropathy

itself. Conversion of fatty marrow into hematopoietically active marrow in induced arthritis of the distal extremities has been observed in rats, and it is speculated that this enhanced myelopoiesis may be due to increased cytokine activity (16,17). Administration of a potent protease inhibitor has been shown to eliminate this exuberant peripheral marrow hyperplasia (16). It is possible that a similar process is part of the Charcot arthropathy.

Bony fractures are an integral part of the neuropathic joint, and the bone marrow is intimately involved in fracture repair. The sequence of steps in new bone formation include formation and maturation of cartilage, invasion of this cartilage by blood vessels and marrow precursors and, finally, formation of both bone and bone marrow (18). There are, in fact, considerable data demonstrating the role of bone marrow transplantation as an aid to healing of fractures (19–21). Hematopoietically active marrow, as part of the fracture repair process, could also explain labeled leukocyte uptake in the uninfected Charcot joint.

Regardless of the underlying mechanism, the end result of such aberrant or atypically located marrow activity, from an imaging standpoint, is a decrease in the specificity of the study, a phenomenon that is now well-recognized (8–10). Interpreting

TABLE 1

Leukocyte/Marrow vs. Leukocyte/Bone in the Charcot Joint

	Leukocyte/ marrow	Leukocyte/ bone*	Leukocyte/ bone†
Sensitivity	2/2	2/2	2/2
Specificity	4/4	0/4	1/4
Accuracy	6/6	2/6	3/6

*Leukocyte activity corresponding to an abnormal area on bone scintigraphy and more intense than adjacent or contralateral marrow activity.

†Spatially incongruent distribution of bone and labeled leukocyte activity or hyperintense activity on the leukocyte image, compared to activity on the bone image.

leukocyte images in conjunction with either traditional bone images or with bone marrow images can reduce the number of false-positive results. The leukocyte/marrow technique has been reported to be the more accurate procedure, however, and the results in this series are in agreement with this observation (9).

CONCLUSION

Although we cannot estimate the frequency with which it occurs, our data demonstrate, as have previous investigations, that uptake of labeled leukocytes does occur in the uninfected Charcot joint. Moreover, this activity does not merely reflect "inflammation"; rather, it represents areas of hematopoietically active marrow, albeit atypical in location, which may be a response to or, perhaps, part of the inflammation, bony destruction and bony remodeling that are part of this entity. Finally, our data illustrate that combined leukocyte/marrow imaging is useful for determining whether or not infection is present in a Charcot joint and that this technique is superior to both leukocyte and three-phase bone scintigraphy, alone or in combination, for this purpose.

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Signal-Enhancing Switched Protocols to Study Higher-Order Cognitive Tasks with PET

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We tested the effectiveness of a switched protocol when it is used to detect signals that result from the study of a higher-order cognitive task with PET. Using language tasks that have been studied extensively in our laboratories, we compared the signal-to-noise ratio (S/N) and statistical significance of the activation signals detected in PET images of regional cerebral blood flow (rCBF), obtained using a standard activation protocol, and of activity concentration, obtained using a switched protocol. **Methods:** Four volunteers were studied with PET while they were performing synonym-generation and word-repetition tasks (activation and baseline tasks, respectively). Each volunteer had three activation/baseline and three baseline/activation scans. Data for each scan were collected in two frames (60 and 120 sec long). During the first 60 sec, data were collected using a standard activation protocol. Subjects then switched tasks, and acquisition continued for 120 sec. Two images were obtained from each scan: an rCBF image using the first frame and an activity-concentration image using both frames. Images were transformed into Talairach space, subtracted and averaged within and across subjects. Parametric t-statistic images were generated for

each protocol, and the magnitude and significance of the activation signals yielded by the two acquisition methods were compared. **Results:** All the activation foci detected using measurements of rCBF were detected when the switched protocol was used; this protocol, in addition, yielded better S/N values. The cognitive component introduced by task-switching in switched protocols did not yield extra statistically significant foci. In single subjects, the average improvement in the signal significance from regions of activation, at a 95% confidence level, was between 6% and 25%. When scans were averaged across subjects, the switched protocol yielded improvements in signal statistical significance of up to 38%. **Conclusion:** We present evidence suggesting that switched protocols can be used to study higher-order cognitive tasks and that they yield activation foci with S/N values that are greater than those of equivalent foci detected using an rCBF protocol. Switched protocols appear to be easy to apply to the testing of higher-order cognitive functions. However, the extra cognitive requirement of switching tasks during data acquisition may be a limiting factor when switched protocols are used to study memory processes.

Key Words: PET; switched protocols; activation studies; oxygen-15-water; cerebral blood flow

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