Indium-111-Labeled White Blood Cells in the Detection of Osteomyelitis Complicated by a Pre-Existing Condition

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Forty-six patients (23M, 23F) ranging in age from 19 to 79 yr with a clinical history of a nonunion fracture, surgery, diabetes or a soft-tissue infection were studied with [^{111}In]oxine WBCs to detect osteomyelitis. There were 27 true-positive, nine true-negative, two false-positive and one false-negative. The false-positives and the false-negative occurred in patients with soft-tissue infections overlying the area of interest. All diagnoses were confirmed by intraoperative bone biopsies and cultures. Bone biopsy and scan were performed within 2 days of each other in 39 patients. The overall sensitivity was 97% (27/28), specificity, 82% (9/11) and the diagnostic accuracy, 92% (36/39). The remaining seven patients had negative [^{111}In]WBC scans several months after positive bone biopsies and definite antibiotic treatment. This suggests that [In]WBC scans become negative after appropriate therapy is undertaken. Interobserver data was obtained from four nuclear physicians of varying experience blinded to clinical information. A high degree of agreement was found in over 90% of the cases. This study demonstrates the utility of [^{111}In]WBC scans in the diagnosis and follow-up of complicated osteomyelitis and a high level of interobserver agreement in scan interpretation.

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The diagnosis of osteomyelitis can be a difficult clinical problem in patients with traumatic injuries, diabetes, recent surgery, or soft-tissue infections. Bone scintigraphy is a valuable tool in the detection of osteomyelitis (*1*), and three-phase bone scanning has added specificity to the technique (*2*). Gallium scanning has also been found to be helpful in some patients (*3,4*). However, gallium localizes in tumors, lymphomas, heterotopic bone and fractures (*5,6*).

Indium labeled white blood cells ([^{111}In]-WBCs) have been shown to accurately predict osteomyelitis in its early and acute stages in both animals and humans (*7, 8*). However, published reports have differed on its value in diagnosing chronic osteomyelitis (*8–10*). Our experience shows [^{111}In]-WBC scans to be valuable and reliable in diagnosing both conditions. In addition, our work has shown that [^{111}In]-WBC studies may be useful in following patients treated for osteomyelitis and predicting the efficacy of treatment.

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MATERIALS AND METHODS

Patient Population

Indium-111 WBC scans were performed in 46 patients ranging in age from 19 to 79 yr over a period of 18 mo. Patients were referred from the Department of Orthopaedic Surgery with a clinical suspicion of osteomyelitis complicating a pre-existing condition. Thirty patients had a history of trauma, six patients had orthopedic devices, three patients had diabetes mellitus, and seven patients had soft-tissue injuries or infections (including one patient with a decubitus ulcer). All patients had an [^{111}In]WBC study, bone biopsy, and culture.

Biopsies were performed in the patients with fractures because of the delayed healing. Patients with positive biopsies were treated with debridement, intravenous antibiotics, and prolonged hospitalization, while patients with negative biopsies had electrical stimulation of their fractures. Other patients were biopsied because of the possibility of osteomyelitis complicating underlying diabetic feet, ulcers, soft-tissue, or painful prosthetic devices. Patients that had scans but no biopsy were excluded. Thirty-nine of the 46 patients had their bone biopsy and culture performed within 2 days of the leukocyte scan.

Studies were interpreted by four nuclear medicine physicians as positive or negative for the presence of osteomyelitis. Positive scans had increased uptake at the area of interest when compared to adjacent bone or the contralateral extremity.

The white cells were a mixed population. A labeling efficiency of 85% was achieved. Dye exclusion testing performed in our hematology department demonstrated >90% viability of the white cells.

Using aseptic technique, 50 ml of venous blood was collected in a 50-ml syringe containing 1 ml heparin and then transferred to a sterile 50-ml polypropylene centrifuge tube working in a laminar flow hood. The red cells were allowed to sediment in the tube for 1 hr or until there was adequate separation of the red blood cells from the remainder of the sample. The supernatant was removed and the red blood cells discarded.

The supernatant was then centrifuged to separate the WBCs from the remainder of the sample, and the leukocytes were incubated with 1,000 μCi [^{111}In]oxine. The free ^{111}In was washed from the preparation and after centrifugation and reconstitution, 250–300 μCi of the labeled WBCs were injected into the patient. This preparation takes ~2 hr.

The patients were imaged at 24 hr postinjection in the anterior projection and, when necessary, in the lateral or posterior projection. Images were obtained with a large field-of-view (LFOV) camera and a medium-energy collimator, using energy peaks of 173 keV and 247 keV. Each site was imaged for 10 min at least. The images were interpreted by four nuclear medicine physicians of varying degrees of experience without any clinical information.

Anaerobic and aerobic bone cultures were obtained on all the patients at the time of bone biopsy. Care was taken in the transport and disposition of the culture specimens and sterile technique was observed meticulously.

RESULTS

The sensitivity was found to be 97% (27/28) and the specificity, 82% (9/11). The overall diagnostic accuracy was 92% (36/39). There were 27 true-positive, nine true-negatives, two false-positives, and one false-negative scan. All 39 scans were performed within 2 days of the bone biopsy. The criteria for a positive scan consisted of focally increased activity compared to the unaffected side and adjacent bone. In some patients it was necessary to obtain lateral views to localize the activity.

Skeletal areas with active bone marrow often gave images that were difficult to interpret. Our high level of diagnostic accuracy may be related to the large number of patients who had conditions involving an extremity which did not have confusing bone marrow activity. Although our overall diagnostic accuracy was 92% which is higher than some reports (*8,10,15*), our results are in agreement with other studies (*10,11,17,18*). Low yield with leukocyte labeling was mentioned as a possible contributing factor to false-negative scans, and perhaps this has adversely affected other results (*18*).

The most common sites of involvement were the tibia (13), femur (3), hip (3), and toes (3), with pelvis (2), foot (2), arm (1), and knee (1) involved less often. The most common microorganism was *Staphylococcus epidermidis*, followed by *Staphylococcus aureus* and *Pseudomonas*. Several patients grew anaerobes and 15 patients grew multiple organisms (Table 1).

Seven patients were studied with [^{111}In]WBC scans several months after their bone biopsies and cultures confirmed the presence of osteomyelitis. Appropriate antibiotic treatment had already been instituted, and clinical resolution had occurred prior to their nuclear medicine studies. In all these patients, [In]WBC scans were negative and confirmed the clinical impression of resolved osteomylelitis. Two of these patients were rebiopsied and confirmed the impression of resolved osteomyelitis.

Interobserver data were correlated from the readings performed by four nuclear medicine physicians, who agreed unanimously on 79% of the cases. Three out of four agreed 13% of the time and in only four cases, two agreed and two disagreed. (The official report was used to decide these cases.) Overall, there was either a majority agreeing (three of four) or unanimous agreement among the physicians in 92% of the cases.

Case Histories

Case 1. A 37-yr-old man fractured his left fibula in a motorcycle accident 1 yr prior to admission. The fracture has been healing poorly, resulting in painful ambulation for the last year. A fixation device was placed with little improvement. He continued to have pain, and the question of chronic osteomyelitis was raised. Radiographs of the ankle disclosed cortical defects in several places where screws had been placed. Some bony sclerosis is seen in the areas around the screws (Fig. 1A). A bone scan disclosed focal uptake in the area of the distal left fibula in the same location as the changes caused by the fixation device on plain film radiographs (Fig. 1B). A labeled [^{111}In]WBC study disclosed no abnormal areas of accumulation of labeled WBCs (Fig. 1C). This study was interpreted as negative for osteomyelitis, and a bone biopsy and culture the next day confirmed this.

Case 2. This was a 79-yr-old woman 4 yr status post left total hip replacement. Two years prior to hospital admission, the patient began noticing some difficulty

TABLE 1
Microbiology Data

Staph epidermidis (17)	*B-hemolytic Strep* (2)
Staph aureus (9)	*Peptostreptococcus* (2)
Pseudomonas (7)	*Enterococcus* (2)
Anaerobes (5)	*Klebsiella* (2)
E. coli (4)	Acinobacter (2)
Enterbacter (3)	*M. Tuberculosis* (1)

Fifteen patients grew multiple organisms in their bone cultures.

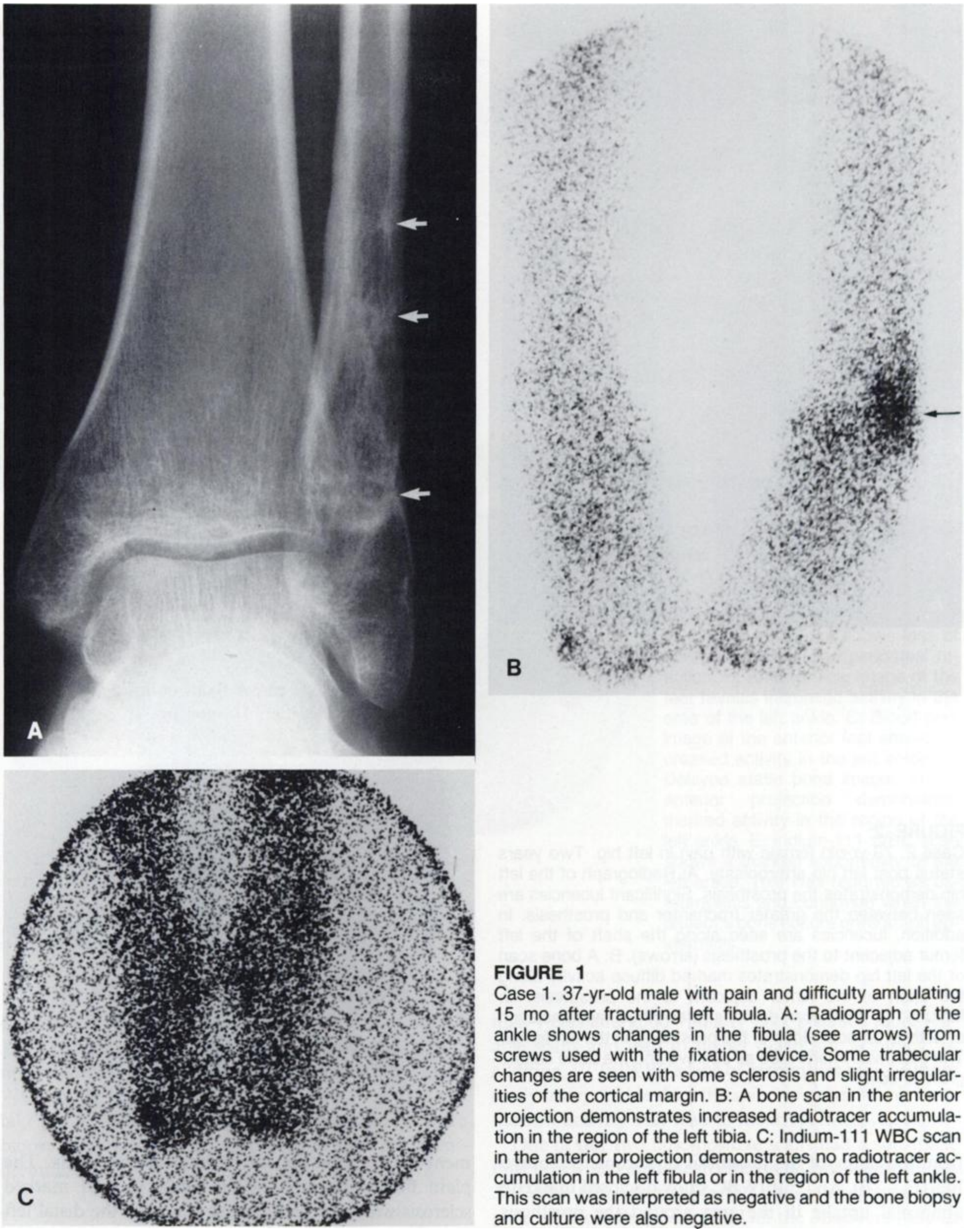

FIGURE 1
Case 1. 37-yr-old male with pain and difficulty ambulating 15 mo after fracturing left fibula. A: Radiograph of the ankle shows changes in the fibula (see arrows) from screws used with the fixation device. Some trabecular changes are seen with some sclerosis and slight irregularities of the cortical margin. B: A bone scan in the anterior projection demonstrates increased radiotracer accumulation in the region of the left tibia. C: Indium-111 WBC scan in the anterior projection demonstrates no radiotracer accumulation in the left fibula or in the region of the left ankle. This scan was interpreted as negative and the bone biopsy and culture were also negative.

in ambulating with her left leg. Pain developed and increased in her left hip, and mobility decreased over the next 2 yr. X-rays showed significant lucencies along the shaft of the prosthesis in the left hip (Fig. 2A). There was also a large lucency between the prosthesis and the greater trochanter. Delayed static images from the bone scan showed diffuse uptake around the prosthesis consistent with diffuse bony irritation which could be either

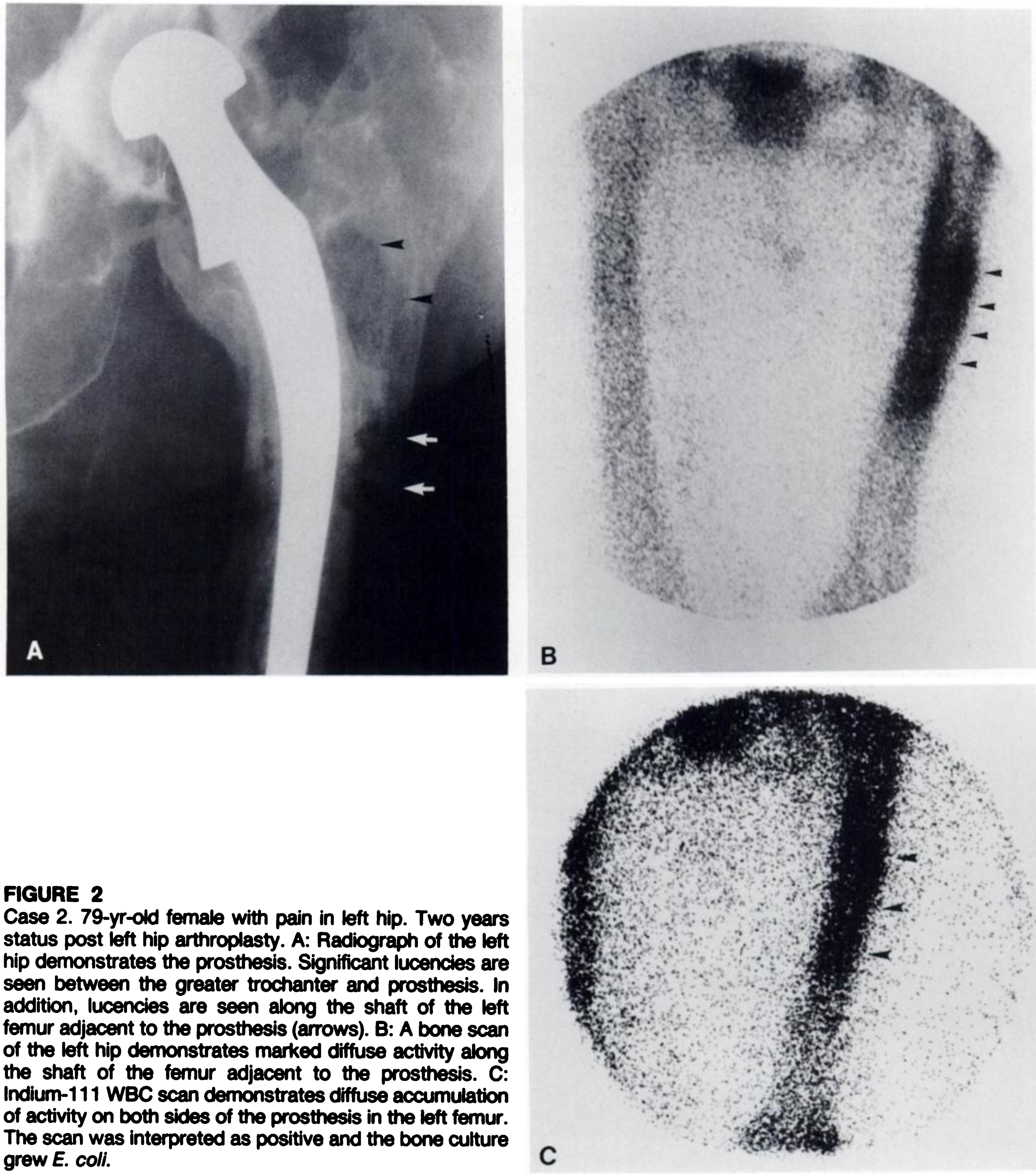

FIGURE 2
Case 2. 79-yr-old female with pain in left hip. Two years status post left hip arthroplasty. A: Radiograph of the left hip demonstrates the prosthesis. Significant lucencies are seen between the greater trochanter and prosthesis. In addition, lucencies are seen along the shaft of the left femur adjacent to the prosthesis (arrows). B: A bone scan of the left hip demonstrates marked diffuse activity along the shaft of the femur adjacent to the prosthesis. C: Indium-111 WBC scan demonstrates diffuse accumulation of activity on both sides of the prosthesis in the left femur. The scan was interpreted as positive and the bone culture grew *E. coli.*

from loosening of the prosthesis or chronic osteomyelitis (Fig. 2B). An [^{111}In]WBC study disclosed markedly abnormal uptake in the area around the prosthesis, which was felt to be typical in appearance for osteomyelitis, and a bone biopsy and culture performed 48 hr later confirmed this (Fig. 2C). The bone culture grew *E. coli.*

Case 3. A 22-yr-old female 2 yr status post a motor vehicle accident was unable to bear weight on her left foot. She had had several hospital admissions and treatment with antibiotics for chronic osteomyelitis. The plain film radiograph of the ankle showed marked sclerosis with periosteal reaction around the distal left tibia. The cortical margins were poorly defined, and the x-ray changes were very suspicious for osteomyelitis (Fig. 3A). Flow images from a bone scan (Fig. 3B) disclosed increased flow to the left ankle. Blood-pool images performed 2–5 min postinjection (Fig. 3C) disclosed increased soft-tissue activity in the area of the left ankle. Delayed static bone images (Fig. 3D) dis-

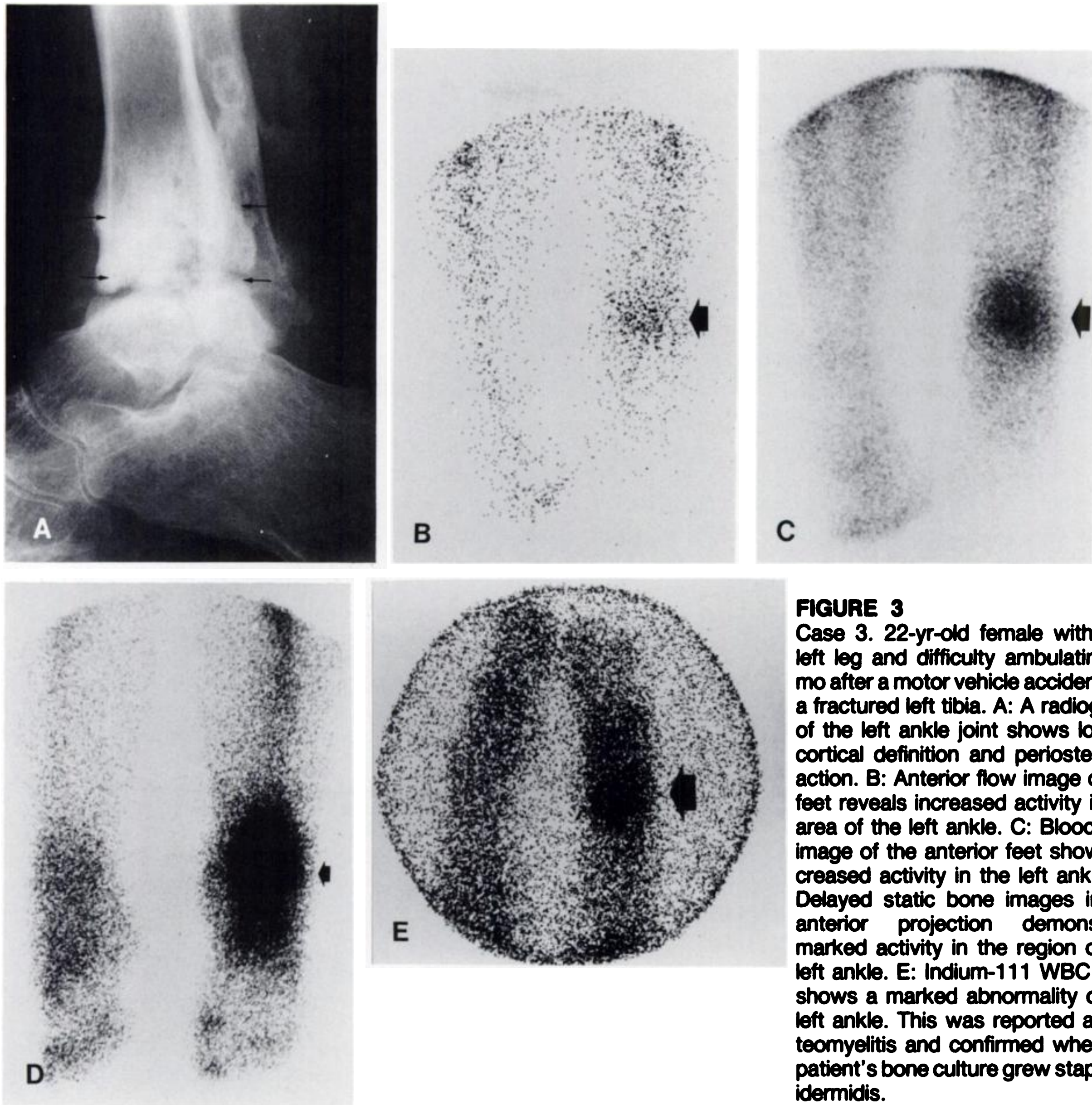

FIGURE 3
Case 3. 22-yr-old female with pain left leg and difficulty ambulating 12 mo after a motor vehicle accident and a fractured left tibia. A: A radiograph of the left ankle joint shows loss of cortical definition and periosteal reaction. B: Anterior flow image of the feet reveals increased activity in the area of the left ankle. C: Blood-pool image of the anterior feet shows increased activity in the left ankle. D: Delayed static bone images in the anterior projection demonstrate marked activity in the region of the left ankle. E: Indium-111 WBC scan shows a marked abnormality of the left ankle. This was reported as osteomyelitis and confirmed when the patient's bone culture grew staph epidermidis.

closed markedly abnormal uptake in the area of the left ankle. These changes all corresponded to the abnormalities seen on the plain film radiographs. The labeled WBC study (Fig. 3E) showed markedly increased uptake in the same area which was confirmed on the bone biopsy and culture. The bone culture grew staph epidermidis.

DISCUSSION

Our work demonstrates a 97% sensitivity with [^{111}In] WBCs in detecting osteomyelitis. Our patients primarily had chronic osteomyelitis, and our success in the diagnosis contrasts with other work (*8*). However, other authors have found good results, similar to ours, with [^{111}In]WBCs (*10,16,17*). White blood cells labeled with high yields and good viability may produce more reliable scans and lead to higher diagnostic accuracy. In addition, [^{111}In]WBC scans of extremities may be more easily interpretable than the spine or pelvis where bone marrow activity may lead to incorrect interpretations.

One of our two false-positive scans had a soft-tissue infection which made scan interpretation more difficult. The other false-positive was in a patient who had undergone a knee arthroplasty, and all the observers were in agreement on the scan interpretation. The false-negative was in a patient with a traumatic fracture of his tibia, and a majority of observers agreed on the scan interpretation.

Gallium scanning has been very useful in diagnosing osteomyelitis, but false-positive scans have been a problem (*3*). Other authors have described gallium uptake in fractures, bones with orthopedic appliances, noninflammatory bone conditions or areas of increased bony activity (*4,11,12*). Still others have suggested that a diffuse pattern or an incongruency between bone and gallium images favors the diagnosis of infection (*11, 12*). Indium-111 WBC scans are easier to interpret and add specificity while retaining the sensitivity of gallium-67. In addition, there was no indication that prior treatment with antibiotics adversely affected the scan results.

In our patients, 23 of 39 were pre-treated with antibiotics. Many of those had undergone broad spectrum antibiotic treatment with cephalosporins, synthetic penicillins, and other i.v. antibiotics which required hospitalization. Some patients had biopsies and scans performed during initial antibiotic therapy while others were scanned and biopsied after completion of a 6-wk antibiotic treatment program. This group had clinical indications for biopsy as a result of persistent pain, fever, difficulty with ambulation, or leukocytosis. Three patients were scanned and biopsied after multiple intravenous antibiotic treatments each requiring hospitalization. In spite of these variables, our findings show that the [In]WBC scan accurately reflected the biopsy findings in these patients with chronic osteomyelitis.

Our experience also showed the value of [In]WBC in predicting the outcome of treatment in osteomyelitis. Indium white blood cell scans in seven patients after treatment for osteomyelitis correctly predicted the clinical outcome. Two were confirmed by repeat bone biopsy and culture while the other five were clinically not felt to be infected over a follow-up period of 1–2 yr.

Prediction of treatment outcome has been tried with gallium in animal models with some success, but gallium scanning still incorrectly predicted the continued presence of osteomyelitis in 40% of the cases (*13*). Our experience shows how valuable [^{111}In]WBC scans can be in obviating further invasive procedures or prolonged hospitalization for antibiotic treatment of possible recurrent osteomyelitis.

There was a high level of agreement (92%) on scan interpretation among those who read the scans. Positive scans were felt to show increased activity at the sites of infection which was more intense than on the opposite or adjacent location. In a few cases, lateral views were required to ascertain whether uptake was present in the bone or in the overlying soft tissue. This has been reported with gallium and was found to be very useful in our study (*14*).

As mentioned in the results sections, disagreement was seen most commonly in the patients with overlying soft-tissue infections. In three of the four patients where a fifth opinion was required, soft-tissue infections were present. Soft-tissue infections remain more difficult to interpret particularly when diffusely increased activity is superimposed over the area of interest. However, [^{111}In]WBC scanning appears to have more promise for diabetic patients with Charcot joints or traumatic bone changes. The three patients in our population with diabetic bony changes were readily distinguished from the osteomyelitis patients.

In conclusion, we found [^{111}In]WBC scans to be sensitive as well as specific in the detection of osteomyelitis. Indium-111 WBC scans can be helpful in patients with trauma, orthopedic prostheses, recent surgery and diabetes. They are less reliable in diagnosing osteomyelitis in the presence of soft-tissue infections, although lateral views are helpful. Possible assessment of therapeutic efficacy by [^{111}In]WBC scans appears promising, but further investigation is necessary. The overall reliability of interpretation is good and lends confidence to the use of this study in the detection and diagnosis of complicated osteomyelitis.

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