Technetium-99m HM-PAO-Labeled Leukocytes in Detection of Inflammatory Lesions: Comparison with Gallium-67 Citrate

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Forty-three patients with suspected benign, inflammatory, or infectious diseases were imaged with [^{99m}Tc]HM-PAO-labeled leukocytes and [^{67}Ga]citrate. Technetium-99m leukocytes showed 22 true-positive, no false-positive, 19 true-negative, and two false-negative findings and [^{67}Ga]citrate 23, 7, 12 and 1, respectively. The sensitivity, specificity, and accuracy values with ^{99m}Tc leukocytes were 92%, 100%, and 95%, and with [^{67}Ga]citrate 96%, 63%, and 81%. Technetium-99m leukocyte scintigraphy has a promising future in comparison with [^{67}Ga]citrate because of the ready availability of [^{99m}Tc]HM-PAO, the good image quality, more rapid results (within few hours), and the lower radiation exposure to the patient with ^{99m}Tc leukocytes. The usefulness of ^{99m}Tc leukocytes in chronic osteomyelitis needs further evaluation.

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Gallium-67 (^{67}Ga) citrate was first shown to accumulate in inflammatory lesions in 1971 (*1*) and thereafter it has been used routinely in the detection of inflammation. In 1976 McAfee and Thakur (*2*) first investigated the use of indium-111 (^{111}In) oxine for the labeling of leukocytes and since then ^{111}In leukocyte scans have been shown to be useful in detection of infections and inflammatory lesions and successfully applied to the evaluation of a variety of pathologic inflammatory conditions (*3,4*). The sensitivity of [^{67}Ga] citrate and ^{111}In leukocytes to detect inflammation is relatively equivalent but increased specificity of ^{111}In leukocytes has made it the procedure of choice (*4*). However, [^{67}Ga]citrate has a greater sensitivity in the identification of prolonged infections of more than 2 wk duration (*5*). Technetium-99m (^{99m}Tc) hexamethylpropyleneamine oxime (HM-PAO) has recently been shown to radiolabel leukocytes in vitro (*6*) and promising results of its clinical use in the identification of inflammatory lesions have been published (*7–11*). Technetium-99m HM-PAO leukocyte method has many advantages over [^{111}In]oxine with respect to image quality, acquisition time, and radiation dose to the patient and it has a promising future as an imaging agent in inflammatory diseases (*9,10,12,13*).

In the present study we have compared [^{99m}Tc]HM-PAO leukocyte and [^{67}Ga]citrate scan findings in a series of 43 patients suspected of having various benign inflammatory conditions.

MATERIALS AND METHODS

Patients

Forty-three patients (27 men, 16 women, age range 25–78 yr, mean age 61 yr) were imaged with [^{99m}Tc]HM-PAO-labeled leukocytes and [^{67}Ga]citrate within 10 days (mean 4 days). The first study was ^{99m}Tc leukocyte scan in 40 cases and ^{67}Ga scan with three patients.

Seventeen patients had suspected bone or joint infection, 11 had suspected prosthetic vascular graft infection, four had suspected inflammatory bowel disease, five had suspected intra-abdominal abscess, five had fever of unknown origin, and one had suspected pulmonary infection. The final diagnosis was confirmed in every case by one or more of the following diagnostic procedures: bacteriologic culture, laboratory tests, histology, standard x-ray procedures, computed tomography, ultrasonography, endoscopy, and bone scan, in combination with clinically relevant signs and favorable response to antimicrobic therapy.

Leukocyte Labeling with [^{99m}Tc]HM-PAO

Mixed leukocytes were isolated and labeled as described previously (*11*). Forty milliliters venous blood was drawn into

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TABLE 1
Results of Imaging with ^{99m}Tc-Labeled Leukocytes and [^{67}Ga]Citrate

Initial diagnosis	^{99m}Tc leukocytes				[^{67}Ga]citrate			
	TP	FP	TN	FN	TP	FP	TN	FN
Bone or joint disease (n = 17)	8	0	7	2	9	2	5	1
Prosthetic vascular graft infection (n = 11)	8	0	3	0	8	1	2	0
Inflammatory bowel disease (n = 4)	2	0	2	0	2	1	1	0
Intra-abdominal abscess (n = 5)	3	0	2	0	3	2	0	0
Fever of unknown origin (n = 5)	0	0	5	0	0	1	4	0
Pulmonary infection (n = 1)	1	0	0	0	1	0	0	0
Total (n = 43)	22	0	19	2	23	7	12	1

a 60-ml plastic syringe containing 10 ml acid citrate dextrose and 10 ml 6% hydroxy ethyl starch to fasten the sedimentation. The erythrocytes were allowed to sediment at room temperature for 1 hr. The supernatant was centrifuged in sterile tubes at 100 *g* for 5 min. The platelet-rich supernatant was separated and centrifuged at 2,000 *g* for 5 min to obtain cell free-plasma. Leukocytes were suspended into 1 ml cell-free plasma. Technetium-99m HM-PAO was formed by adding 600 MBq ^{99m}Tc in 6 ml isotonic saline to a vial containing HM-PAO (Ceretec, Amersham International). Five milliliter (500 MBq) of [^{99m}Tc]HM-PAO-complex was added to the leukocyte suspension which was left for 10 min at room temperature. The cells were repelletted at 100 g for 5 min, resuspended in 5 ml cell-free plasma, and reinjected intravenously. The cell labeling efficiency was 39% (range 18–72%).

Scintigraphy and Analysis of Scintigrams

Planar images were obtained at 0.5 hr, 2 hr, 4–6 hr, and 18–24 hr after the injection of ^{99m}Tc leukocytes, and 24–72 hr after the administration of 110–185 MBq of [^{67}Ga]citrate. Two nuclear physicians interpreted the images without the knowledge of clinical diagnosis. The intensity of uptake was graded as weak, moderate, or strong by subjective evaluation. On rare occasions when the readings differed, the final result was obtained by consensus. A scintigram was considered "true positive" when the pathologic uptake was caused by a benign inflammatory or infectious disease confirmed by other diagnostic procedures mentioned earlier. A positive scintigram was considered "false positive" when the finding was verified to be noninfectious and noninflammatory by other diagnostic modalities. A negative scintigram was considered "true negative" when no focal infectious or inflammatory benign process was found, and "false negative" when a focal infectious or inflammatory process was found by other diagnostic procedures.

RESULTS

The results of the scintigraphic examinations are presented in Tables 1 and 2. The sensitivity of [^{67}Ga] citrate was a little better than that of ^{99m}Tc leukocytes but ^{99m}Tc leukocyte scan showed much greater specificity, accuracy, and positive predictive value.

The normal distribution of the activity in ^{99m}Tc leukocyte scan was similar to that seen with ^{111}In-labeling with exception of urinary bladder visualization in all patients. The normal distribution has been described in detail previously (*6,8,9,12–14*).

All patients with true positive findings in inflammatory or infectious disease, showed abnormal uptake even at 0.5 hr after injection of ^{99m}Tc leukocytes and the intensity of uptake increased in later images. The final diagnoses of the 17 patients with suspected bone or joint infection were four acute, two subacute, and three chronic osteitis or prosthetic joint infection; two metastatic malignancies, one reactive arthritis, and five with no inflammatory or malignant bone disease. Eight were true positive with ^{99m}Tc leukocytes and nine with [^{67}Ga]citrate. Results in acute and subacute infections were comparable. Two patients with bone metastases, one from lung carcinoma and the other from malignant melanoma had true-negative ^{99m}Tc leukocyte scans but false-positive [^{67}Ga]citrate scans. Two patients with chronic osteomyelitis showed false-negative ^{99m}Tc leukocyte scans but positive [^{67}Ga]citrate scans, however, one patient with chronic osteomyelitis was negative with [^{67}Ga]citrate but positive with ^{99m}Tc leukocytes. One patient with bacteriologically verified subacute prosthetic hip joint infection was moderately positive with ^{99m}Tc leukocytes but only weakly positive with ^{67}Ga citrate (Fig. 1).

All prosthetic vascular graft infections were positive with both agents and the information obtained was relatively comparable (Fig. 2). In addition there was

TABLE 2
Sensitivity, Specificity, Accuracy, and Predictive Values of ^{99m}Tc Leukocyte and [^{67}Ga]Citrate Scintigraphies in the Detection of Benign Infectious or Inflammatory Diseases

	^{99m}Tc leukocyte	[^{67}Ga]citrate
Sensitivity (%)	92	96
Specificity (%)	100	63
Accuracy (%)	95	81
Positive predictive value (%)	100	77
Negative predictive value (%)	90	92

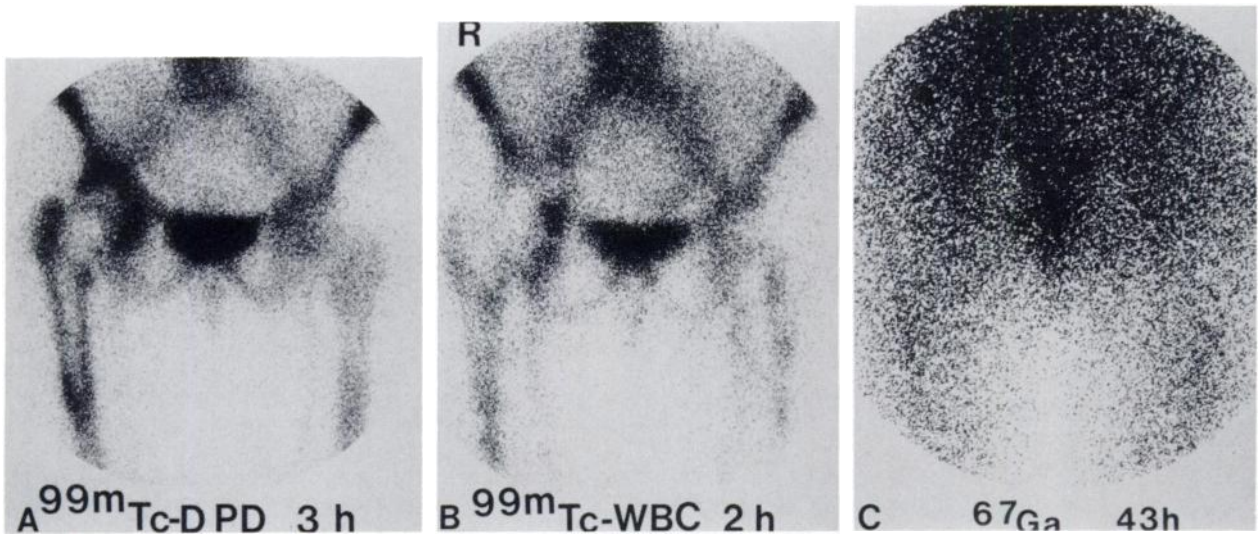

FIGURE 1
Infected prosthetic hip joint shows marked abnormal activity in bone scan (A) and ^{99m}Tc leukocyte scan (B) and weak abnormal activity in [^{67}Ga]citrate scan (C).

one false-positive aortic graft prosthesis with [^{67}Ga] citrate but ^{99m}Tc leukocyte scan showed a true-negative result.

Two patients with suspected inflammatory bowel disease had colonic diverticulitis somewhat more positive with ^{99m}Tc leukocytes than with [^{67}Ga]citrate. The para-aortic pathologic nodes of a patient with Hodgkin's disease were weakly false positive with [^{67}Ga] citrate but negative with ^{99m}Tc leukocytes. Three intra-abdominal abscesses were true positive with both agents (Fig. 3). Two patients with suspected abdominal abscesses had malignant diseases: splenic lymphoma and abdominal metastases of an adenocarcinoma of unknown origin, which showed uptake of [^{67}Ga]citrate but were negative with ^{99m}Tc leukocytes.

All patients with fever of unknown origin were true negative with ^{99m}Tc leukocyte scan but one patient with multiple bone metastases of lymphoma showed strong uptake of [^{67}Ga]citrate (Fig. 4). The pulmonary infection was bacteriologically verified tuberculosis and showed focal uptake in the left lung with both agents but the ^{99m}Tc leukocyte uptake was greater.

DISCUSSION

The sensitivity, specificity, and accuracy of ^{99m}Tc leukocyte scan were 92%, 100%, and 95%. The values are similar to a recent article by Roddie and collegues (*9*). In their study 100 patients suspected of having various inflammatory diseases were imaged with [^{99m}Tc] HM-PAO-labeled leukocytes and 100% sensitivity and 95% specificity were found. In the present study [^{67}Ga] citrate showed 96% sensitivity, but the specificity and accuracy values were lower, 63% and 81%, respectively, which agree with other studies with [^{67}Ga]citrate in various inflammatory conditions reviewed by Froelich (*4*).

The image quality of ^{99m}Tc leukocyte scans was better than the quality of [^{67}Ga]citrate scans and most, although not all, pathologic processes were better deline-

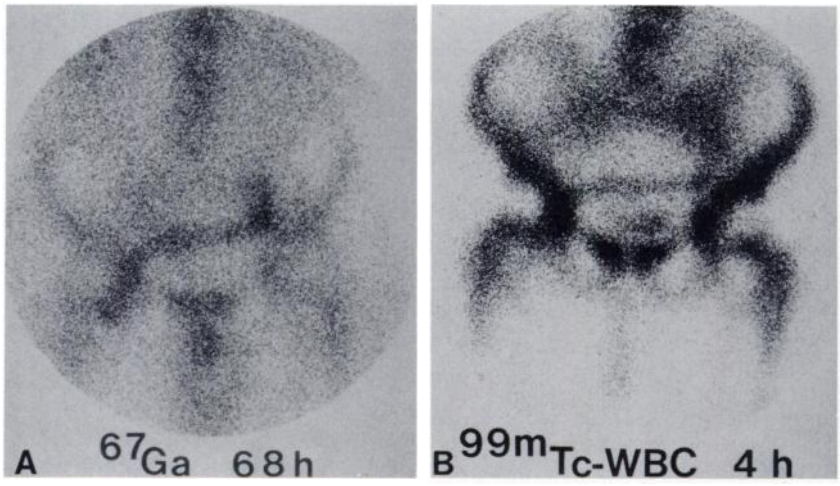

FIGURE 2
Iliofemoral prosthetic vascular graft infection is somewhat better visualized with [^{67}Ga]citrate (A) than with ^{99m}Tc leukocytes (B).

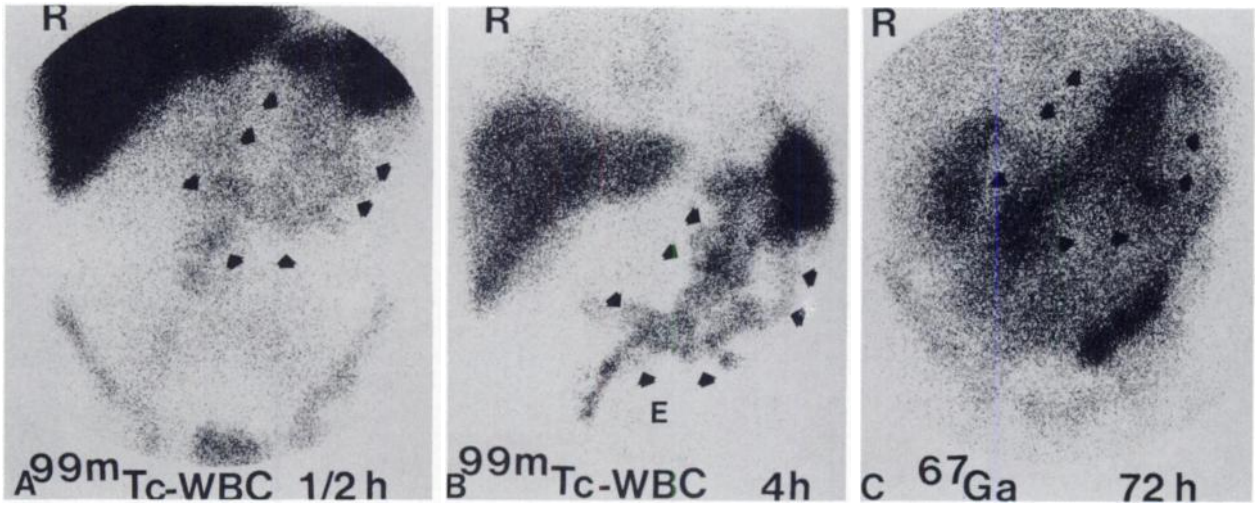

FIGURE 3
Abdominal abscess with multiple cavities is visualized with ^{99m}Tc leukocytes at 0.5 hr after injection (A), the uptake is increased at 4 hr and the abscess is sharply delineated from the background activity (B). The quality of the [^{67}Ga]citrate image at 72 hr is much poorer (C).

ated with ^{99m}Tc leukocytes. The difference in the image quality between these two agents was most conspicuous in the abdominal region. Weak to moderate activity in the gut was always seen in the [^{67}Ga]citrate scan in spite of bowel cleansing before imaging. There was only minimal background activity in the bowel up to 4–6 hr with ^{99m}Tc leukocytes but nonspecific bowel activity was seen in some patients in the 6 hr image and large bowel was always at least weakly visualized at 18–24 hr. We suggest that patients with suspected inflammation in abdominal region should be imaged during the first 4 hr after the administration of ^{99m}Tc leukocytes to avoid false-positive finding as was also suggested by others (*7,9,12*).

Technetium-99m leukocytes showed no false-positive finding whereas there were seven false-positive [^{67}Ga]citrate scans. One of these patients had an old noninflammatory and noninfected resolving para-aortic hematoma. The other six were various malignancies, which were negative on ^{99m}Tc leukocyte scan. Most bone metastases were seen as defects on ^{99m}Tc leukocyte scan. Such a defect in skeleton is not a specific sign of malignancy, however, because two false-negative chronic osteomyelitis showed similar defects. Although all malignancies were true negative with ^{99m}Tc leukocytes and no false-positive finding has been described so far in the literature, it is probable that some malignancies will accumulate ^{99m}Tc leukocytes since some positive findings have been described using ^{111}In leukocytes (*15–20*).

The only false-negative finding with [^{67}Ga]citrate was found in chronic osteomyelitis. Gallium-67 citrate has been described to be very useful and superior to ^{111}In leukocytes in chronic bone infections (*4,15,21*) although good results with ^{111}In leukocytes have also been reported (*22,23*). Our results with ^{99m}Tc leukocytes were good in suspected bone or joint infection except with two of three patients having chronic disease. More evaluations with ^{99m}Tc-labeled leukocytes are needed to make conclusions of the usefulness of this agent in chronic bone infections. In acute and subacute bone and joint diseases ^{99m}Tc leukocytes gave reliable infor-

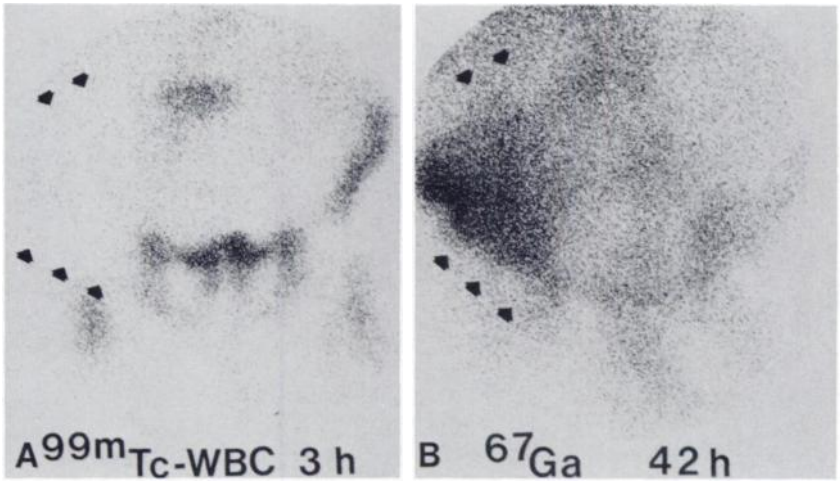

FIGURE 4
Anterior images of pelvis in a patient with metastatic lymphoma in right iliac bone. Large defect is seen in ^{99m}Tc leukocyte scan at 3 hr (A) and strong uptake in [^{67}Ga]citrate image at 42 hr (B).

mation which is in agreement with some previous studies with ^{111}In leukocytes (*15,21*).

Both ^{99m}Tc leukocytes and [^{67}Ga]citrate scan were found to be very reliable in detecting prosthetic vascular graft infection, which agrees with results described previously (*24–26*). All five patients with fever of unknown origin were true negative with ^{99m}Tc-labeled leukocytes. It has been shown previously that there is very low frequency of detectable infection in this clinical situation (*27*).

Recent comparisons of ^{99m}Tc leukocytes and ^{111}In leukocytes have shown the ^{99m}Tc method equal or better than the ^{111}In method and the quality of images has been better in ^{99m}Tc-labeled leukocyte scan (*6,7,10,12, 13*). Technetium-99m leukocytes were also superior to iodine-123-labeled monoclonal antibodies against granulocytes in a recent study (*14*).

In conclusion, [^{99m}Tc]HM-PAO-labeled leukocyte scintigraphy seems a very useful tool in the diagnosis of various infectious and inflammatory processes. Both the ^{99m}Tc and HM-PAO kit are readily available even for emergency use in many countries. The quality of ^{99m}Tc leukocyte image is superior to that of [^{67}Ga]citrate and ^{111}In leukocytes, the result is available more rapidly, and the radiation dose to the patient is lower (*8,12*). The usefulness of this method in chronic osteomyelitis and possibly in other chronic diseases needs further evaluation.

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