Technetium-99m-Labeled Anti-Granulocyte Antibodies in Suspected Bone Infections

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The introduction of ^{99m}Tc-labeled anti-granulocyte antibodies seemed to provide advantages in comparison with formerly used in vitro methods to label autologous white blood cells for inflammation imaging. For this reason, we have undertaken a study to evaluate the clinical significance of this method. Thirty unselected patients with suspected bone infections were studied prospectively using the monoclonal ^{99m}Tc-labeled anti-granulocyte antibody. Twenty patients were referred with suspected infections of the peripheral bones (Group I), as well as 10 patients with suspected infections of the spine (Group II). Planar whole-body scans were performed 4 hr and 20 to 24 hr after administration of 500 MBq of the labeled antibody. Scans were considered positive for a bacterial (septic) infection when a focally increased antibody accumulation occurred. All scans were evaluated in blinded fashion by two experienced readers. Of the 20 studies from Group I patients, four false-positive scintigraphic findings were observed, and one false-negative, resulting in a specificity of only 64% and a sensitivity of 89%. In Group II (10 studies), five scans were true-negative, and five false-negative. For both groups, the specificity of the scintigraphic method was quite low (75%), and the sensitivity was also relatively low (57%). The results of this study demonstrate that in an unselected patient population in whom the diagnosis is not known, scintigraphy with ^{99m}Tc-anti-granulocyte antibodies is not a reliable method for detecting septic inflammatory lesions. In addition, use of this method excludes septic lesions with only a moderate likelihood (83% negative predictive value).

J Nucl Med 1992; 33:526-531

The current diagnosis of inflammatory diseases using imaging modalities frequently employs imaging with radiolabeled leukocytes in addition to conventional methods such as x-ray, CT, and radionuclide bone scanning (*1-11*). The aim of these diagnostic efforts is to detect and verify septic inflammatory disease as early as possible after the initial clinical suspicion.

Received Aug. 12, 1991; revision accepted Nov. 21, 1991.

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The procedure for labeling white blood cells (leukocytes, granulocytes) with radioactive tracers has changed significantly over the last few years. The separation and radiolabeling of mixed leukocytes with ^{111}In-oxine was first introduced into clinical medicine by Thakur et al. (*12*) in 1976. This approach is still considered the "gold standard" for the detection of septic inflammation lesions. A method to label blood cells with ^{99m}Tc-HMPAO became available in 1986 (*13*), and since 1987/88 a monoclonal murine antibody against human granulocytes has been available for clinical trials (*14,15*).

Labeling with both ^{111}In-oxine and ^{99m}Tc-HMPAO has some disadvantages, including the relatively time-consuming separation procedure and the unfavorable physical properties of ^{111}In for gamma camera imaging. The introduction of ^{99m}Tc-labeled monoclonal anti-granulocyte antibodies (AGAB) thus seemed to be an advantage over the former modalities which involve cell separation.

The aim of this study was to evaluate whether the use of these AGABs would also provide more precise information on questionable bone infections. Furthermore, we were interested in evaluating the sensitivity and accuracy of inflammation imaging using this antibody. We therefore initiated a clinical study in orthopedic patients with equivocal bone infections including both peripheral bones and the spine.

MATERIALS AND METHODS

The AGAB used for this study was produced and supplied by Behringwerke AG (Frankfurt, Germany). The AGAB is an immunoglobulin of the IgG isotype with a molecular weight of 150,000 daltons and binds to the carcinoembryonic antigen (CEA), an epitope on the granulocyte surface that is expressed at the nonspecific cross-reacting antigen, NCA-95. The affinity constant of the antibody is 2×10^9 liter/mol/granulocyte. The lyophilized antibody can be readily labeled with ^{99m}Tc in a one-step procedure. The in vivo binding of AGAB to granulocytes is greater than 90%. Granulocyte function is not altered, since there is neither cell-mediated cytotoxicity nor complement-mediated cytotoxicity by antibody-binding to the granulocyte. The labeling procedure was as follows: The average activity to label one vial of lyophilized antibody for one patient was 500 MBq of ^{99m}Tc, and the labeling efficiency was >95% in all trials (thin-layer

chromatography). After a 10-min incubation period, the labeled antibodies were injected into the patient. Other workers have reported the development of HAMAs (human anti-mouse antibodies) in 22% of all patients after an average period of 7–8 wk following the injection of AGAB (*15*). No side effects or adverse reactions following the injection were observed in any of our patients.

Planar whole-body images were obtained 2 (early images) and 4 hr and 20 to 24 hr (delayed images) postinjection, respectively, and 500,000 counts per image were collected. The scans were obtained on a LFOV gamma camera equipped with an all-purpose collimator connected to a computer (Apex 409 A, Elscint).

The normal antibody distribution is characterized by the visualization of the entire bone marrow, liver and spleen (delayed images). In addition, blood-pool activity (e.g., major vessels) is visible on the early images. Together with the results of the delayed images, the early images representing vascular structures were helpful in determining the effect of nonspecific blood-pool radionuclide accumulation in the final evaluation of the respective scan.

All scintigrams were evaluated by two experienced readers who knew neither the results of other imaging modalities nor the clinical status of the patients. Scans were considered positive for a bacterial (septic) infection when a focally increased antibody accumulation could be visualized. Only these findings were taken as positive findings for infection. So called "cold lesions" (e.g., defects) were considered negative for infection.

Patients

Thirty-three patients were studied (23 male, 10 female), ranging from 15 to 70 yr of age with an average age of 47 yr. Infection of the extremities was suspected in 23 patients (Group I), and 10 patients were referred with suspected infection of the spine (Group II) (Table 1).

All patients who were studied scintigraphically had previously suspected spondylitis and osteomyelitis of the peripheral bones. Only those patients were included in the study for whom the final diagnosis of osteomyelitis had been either established by histology, microbiology and radiology, or had been excluded from a longstanding clinical course. The suspected areas were investigated by planar x-ray in all patients and T-CT studies were performed in 18 patients. All AGAB scans were evaluated at the time of scintigraphy without knowledge of the final diagnosis.

Hence, by these criteria, 30 patients could be included into the study who had a final diagnosis by means other than scintigraphic methods (Group I: 20 patients, Group II: 10 patients).

TABLE 1A
Localization of Questionable Bone Infections

Location and Number of Lesions			
Extremities		Spine	
Hips	4	Thoracic	3
Knee joint	5	Lumbar	7
Tibia	3		
Foot	6		
Femur	3		
Humerus	1		
Clavicula	1		
Total	23		10

RESULTS

The diagnosis of a septic (bacterial) bone infection could be established by surgery and histopathology in 9 of 20 Group I patients (extremities) and in 5 of 10 Group II patients (spine). In 11 Group I patients and in 5 Group II patients, an infection could be excluded by the subsequent clinical course.

Patients

Group I (Patients with Suspected Osteomyelitis of the Peripheral Bones, Table 2). In eight Group I patients, AGAB accumulations were visualized on the bone scans. These findings were in agreement with the final diagnosis of osteomyelitis (eight true-positive scintigraphic findings). An example of a true-positive finding is illustrated in Figure 1.

The AGAB studies revealed no abnormalities in seven patients and were finally considered to be true-negative with respect to the clinical course. Three of these patients were on oral antibiotic therapy at the time of scintigraphy.

Four AGAB scans showed antibody-leukocyte accumulations that were interpreted as infectious lesions, but the clinical follow-up could not confirm the diagnosis of osteomyelitis (four false-positive scintigraphic findings). Three of these patients were on oral antibiotic therapy at the time of scanning. These false-positive scans occurred in one patient with osteoporosis due to inactivity of the left knee joint following trauma. One patient had a reactive synovitis after hemarthrosis in hemophilia A (Fig. 2). The third patient had a (non-bacterial) synovitis of the talonavicular joint, and the fourth patient had an acute attack (episode) of Bechterew's disease with pain symptoms in the right foot in which AGAB accumulation was noted.

In one patient with known chronic left coxitis, the AGAB scan showed a defect (cold lesion) at the left hip joint (Fig. 3). This scan was considered negative. From this patient's radiograph, a bone infection was suspected, and a joint puncture confirmed a bacterial infection by

TABLE 1B
Age of Suspected Infection and Final Scintigraphic Results

I. Suspected Peripheral Infections (n = 20)					
Years		0.5–1	1–3	3–5	>5
Final results	T+	3	2	—	3
	T−	4	2	1	—
	F+	2	2	—	—
	F−	—	1	—	—
II. Suspected Central Infections (n = 10)					
Years		0.5–1	1–3	3–5	>5
Final results	T+	—	—	—	—
	T−	—	2	1	2
	F+	—	—	—	—
	F−	1	1	1	2

T+; T−: true-positive; true-negative.
F+; F−: false-positive; false-negative.

TABLE 2
Results for Group I Patients (n = 20) with Suspected Infection of Peripheral Bones

Final diagnosis*	^{99m}Tc-AGAB scans +	−	All
Septic infection	8	1	9
No septic infection	4	7	11
Total	12	8	20

Sensitivity = 89%, specificity = 64%, accuracy = 75%, PPV = 67%, and NPV = 88%.

* All diagnoses based on histopathology (biopsy or surgery) or on long-standing clinical course.

+: Focally increased ^{99m}Tc-AGAB accumulation.

−: Normal findings on ^{99m}Tc-AGAB scans.

the detection of *enterococcus* bacteria (one false-negative scan).

From these results a sensitivity of 89%, a specificity of 64%, an overall accuracy of 75%, a negative predictive value of 88% and a positive predictive value of 67% were calculated for AGAB scanning in patients with suspected peripheral bone infections.

Group II (Patients with Suspected Spondylitis, Table 3). This group consisted of 10 patients with suspected spine infections. Four of these patients were on antibiotic treatment at the time of scintigraphic investigation. The scintigrams did not show increased AGAB accumulation at the site of the suspected infection in any of these patients. Five AGAB scans were true-negative, from which three patients were found to have slightly decreased AGAB accumulation at the suspected vertebra. One of these patients had a previously healed spondylitis, one a high-grade (severe) osteochondrosis, and the third patient presented with a healing fracture. Septic infection could be excluded in all of them by the subsequent clinical course and the results of other (x-ray based) investigations.

The remaining two scans showed no abnormalities (normal AGAB accumulation within the bone marrow). One of these patients had a nonspecific spondylitis, and the other had been diagnosed as having a healed tuberculotic spondylitis.

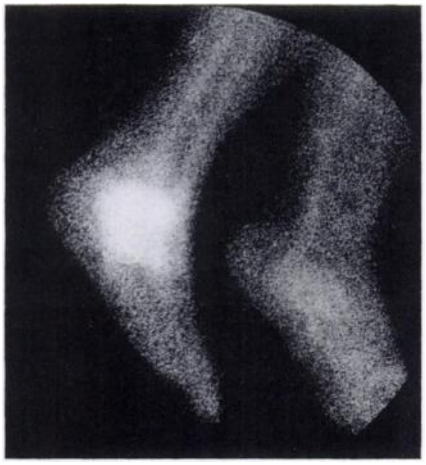

FIGURE 1. True-positive ^{99m}Tc-AGAB scan. This patient had a history of arthrodesis of the right ankle joint and subsequent chronic pain. Biopsy revealed a chronic osteomyelitis.

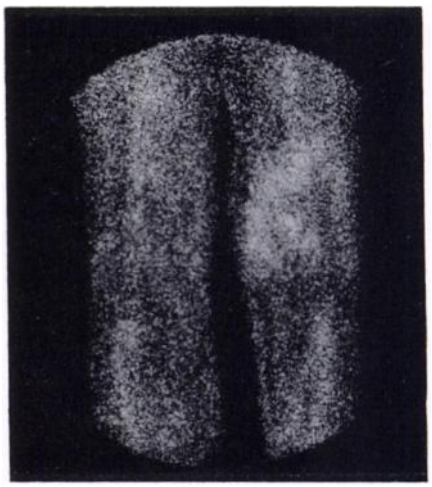

FIGURE 2. False-positive ^{99m}Tc-AGAB scan. This patient with Hemophilia A (since 1964) and HIV positive (since 1989) presented with complaints of the left knee joint. X-ray and laboratory investigations showed normal findings. Left knee joint puncture revealed an aseptic, reactive synovitis following hemarthrosis.

Due to the study protocol, five AGAB scans were considered false-negative since there was not an increased but a focally decreased activity detectable at the site of the suspected vertebrae. Of these five patients, one patient presented with post-traumatic spondylitis, two with spondylitis of unknown origin and two with tuberculotic spondylitis. Three patients were treated with antibiotics. All patients were finally diagnosed as having bacterial infection by surgery and histopathology.

Comparison of Group I and II Results

For all patients (Table 4), the sensitivity of AGAB scanning to detect a septic infection was 57%, the specificity 75%, the accuracy 67%, and both the positive and the negative predictive value were 67%.

Excluding patients with "cold lesions", one could calculate the following values: sensitivity and specificity: 89%, accuracy: 76%, positive predictive value: 67%, negative predictive value: 89%.

For "cold lesions" as "true-positive" findings (despite the initial evaluation), the following values would have been calculated: sensitivity: 94%, specificity: 67%, accu-

TABLE 3
Results for Group II Patients (n = 10) with Suspected Spine Infections

Final diagnosis*	^{99m}Tc-AGAB scans +	−	All
Septic infection	0	5	5
No septic infection	0	5	5
Total		10	10

* All diagnoses based on histopathology (biopsy or surgery) or on long-standing clinical course.

−: Slightly decreased activity and cold lesions.

TABLE 4
Results for Group I and II Patients (n = 30)

Final diagnosis	^{99m}Tc-AGAB scans +	−	All
Septic infection	8	6	14
No septic infection	4	12	16
Total	12	18	30

Sensitivity = 57%, specificity = 75%, accuracy = 67%, PPV = 67%, and NPV = 67%.

racy: 83%, positive predictive value: 81%, negative predictive value: 89%.

All infectious lesions were clearly visualized on both the early scans (4 hr p.i.) and the delayed scans (24 hr p.i.). There were no changes in lesion activity patterns nor were there visible changes concerning the normal activity distribution between the 4- and 24-hr p.i. scans.

DISCUSSION

The in vitro labeling of AGAB with ^{99m}Tc was easy, and the entire labeling procedure required an average time period of 20 min. This short time period represents an enormous advantage compared to the time-consuming procedure of blood cell isolation and labeling, as is necessary using the conventional ^{111}In or ^{99m}Tc-HMPAO methods.

Bone and bone marrow scans were not part of the study protocol since there were concerns that not all those modalities could have been performed within a time period sufficient to ensure an accurate comparison of the results. In most of the patients, however, we performed either bone or bone marrow scans, usually a couple of months prior to or after the time the patient entered the study. Since we designed a prospective blinded study to evaluate the significance of AGAB scanning, these results were not included in this study.

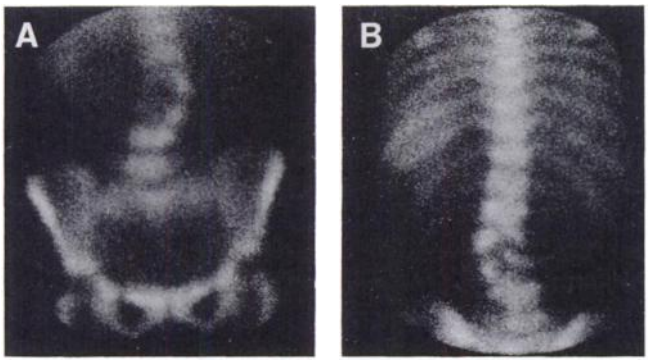

FIGURE 3. False-negative ^{99m}Tc-AGAB scan ("cold lesion") of a patient with a history of suspected spondylodiscitis and pain. X-ray and T-CT showed destruction of lumbar vertebra 2 and 3 and biopsy-confirmed spondylitis and paravertebral abscess with *E. coli* bacteria. (A) Ventral view and (B) dorsal view.

The in vivo distribution of ^{99m}Tc-AGAB is quite similar to that of ^{111}In-labeled leukocytes and visualizes the entire bone marrow RES as well as the liver and spleen RES (*10*). In contrast to leukocyte imaging using ^{99m}Tc-HMPAO labeled white blood cells, no nonspecific activity was observed within the gastrointestinal tract. AGAB imaging would thus be applicable for detection of possible abdominal infections. In a previous study (*10*), we compared inflammation imaging using antibodies, conventional mixed white blood cells and nanocolloid in patients with suspected peripheral infections. In this study, all three methods showed almost identical scintigraphic findings. We also attempted to establish a quantitative measure (e.g., count ratios between affected and nonaffected extremity, count ratio between lesion and background) which would enable a differentiation between more acute or chronic infections. These attempts, however, failed to provide a sufficient high correlation (*31*).

The visual comparison of the 4-hr and the delayed AGAB scans in our study did not show significant differences of activity distribution (except blood-pool activity on the early images) on either image so that a diagnosis could be sufficiently established from the scan taken 4-hr postinjection. This situation has also been suggested by Joseph and coworkers (*16*), who demonstrated all infected lesions at 2–6 hr following injection.

For patients in our study, irrespective of peripheral or spinal infections, the sensitivity and specificity were relatively low with values of 57% and 75%, respectively. These results are in contrast to some former studies which reported a sensitivity of 75%–100% and a specificity of 89%–100% for detecting bone infections (*17–21*).

Using the data for those patients with peripheral infections in our study, the sensitivity would be 89% with a specificity 64%. Even these values, however, are still lower than those reported in the literature. We believe that these differences are not related to cell alteration in the labeling procedure. Bosslet et al. (*21*) recently demonstrated that the in vivo affinity of the labeled antibody to granulocytes is absolutely specific and that the vital and functional properties of granulocytes are not altered by the immunoreaction with the labeled antibody in vivo.

These discrepancies may result from different imaging agents and the selection of the patient groups since some authors still use the ^{111}In and ^{99m}Tc-HMPAO in vitro labeling techniques (*17,21*). A major part of the data, reported in the literature, however, was based on preselected patients with bone infections prior to the scintigraphic study. Our study, in contrast, consisted of an unselected patient group, which means that the patients had not been referred with a previously known infection for AGAB scanning. We therefore believe that the results of our study better reflect the ability of inflammation imaging with AGAB to detect a septic infection.

For the patients with suspected peripheral infections, there were four false-positive scintigraphic results that

occurred in aseptic synovitis, Bechterew's disease and osteoporosis. Aseptic osseous and arthrogenous inflammations as well as osseous healing processes can be accompanied by leukocyte and phagocytic cell accumulation which then leads to false-positive scintigraphic findings using both labeled mixed cell preparations and in vivo labeled granulocytes. Previous studies also have reported false-positive findings using ^{111}In and ^{99m}Tc-HMPAO labeled mixed cell preparations (*6, 23–27*). Possible reasons for false-positive findings can be also seen in granulomas and in malignant tumors. We believe that the relatively low specificity of AGAB scintigraphy does not allow for the differentiation of an aseptic infection, nonspecific arthritis, osteotomy or fracture healing from septic bone or joint infections. We also believe that previous studies in part reported high specificity for mixed cell preparation imaging due to the preselection of patients and hence to a high prevalence of the symptom "osteomyelitis."

In none of our patients with suspected spondylitis (n = 10) could we detect AGAB accumulation. On the contrary, in four of five patients with proven spondylitis, the AGAB scan revealed a lesion instead of an expected accumulation.

This phenomenon of false-negative findings in spondylitis has been reported in some studies (*5,7,19,28*). It may be speculated that this observation is related to the age of the infection. In a recent study, Palestro et al. (*32*) reported positive scintigraphic findings using ^{111}In-labeled leukocytes in patients with spondylitis who presented within a short time period after the occurrence of symptoms (mean: 2 wk). In our study, the patients were investigated later (mean: 20 mo).

In an animal model (*29*), the possible reasons for the nonvisualization of septic spondylitis on leukocyte imaging have been investigated. From these data two types of decreased leukocyte uptake can be considered: (a) decreased blood flow (and decreased cell delivery) due to an extended fibrosis of the medullary space in chronic (longer standing) spondylitis, and (b) abscess with development of a peripheral connective-tissue membrane which then causes diminished leukocyte migration into the central and peripheral areas of the abscess. We also observed a cold lesion (decreased cell accumulation) in a patient with osteochondrosis without any signs of inflammation that could be caused by destruction of the bone marrow. In a recent study, Sciuk et al. (*30*) have compared inflammation imaging with AGAB and ^{99m}Tc-HIG (modified human immunoglobulin) in 17 patients with chronic osteomyelitis of peripheral and central bone structures. In their study, they stressed that cold lesions in the spine can occur in the destruction of bone marrow by other than inflammatory diseases, such as bone marrow metastases. They conclude that, with respect to central lesions, HIG scintigraphy seems to be more specific, whereas in peripheral lesions the AGAB scans seem to provide better results.

One can assume that the mechanisms for the phenomenon of cold lesions in central inflammation, especially in the spine, are based on a circumscribed fibrotic destruction of bone marrow or decreased leukocyte migration due to the membranous wall of an abscess.

In general, however, for the evaluation of a leukocyte study, regardless of the agent used, one has to consider a completely different behavior of the labeled cells for peripheral and central infections.

In conclusion, our results indicate that ^{99m}Tc-AGAB is not a suitable agent for detecting inflammatory diseases of the spine. For questionable infections of the peripheral osseous structures, ^{99m}Tc-AGAB scintigraphy has a relatively low specificity (64%) and a moderate sensitivity of 89%. Thus, only unequivocal normal findings of peripheral bones on the AGAB scan excludes a septic inflammation with a moderate likelihood since the negative predictive value is 83%.

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