Technetium-99m-HMPAO-Labeled Leukocytes and Technetium-99m-Labeled Human Polyclonal Immunoglobulin G in Diagnosis of Focal Purulent Disease

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To evaluate the usefulness of ^{99m}Tc-HMPAO-labeled leukocytes and ^{99m}Tc-labeled polyclonal human immunoglobulin G (Technescan HIG) in the diagnosis of focal purulent disease, 31 comparative scintigraphies were done in 30 patients with known or strongly suspected focal infection. Focal purulent disease was the final diagnosis in 19 patients. Technetium-99m-labeled leukocytes showed 16 true-positive, no false-positive, 11 true-negative and 3 false-negative findings. The corresponding figures for ^{99m}Tc-labeled HIG were 11, 2, 9 and 8. The sensitivity and specificity of imaging with labeled leukocytes were 84% and 100%, respectively, and with labeled HIG, 58% and 82%, respectively. The overall accuracy of the leukocyte scan was significantly better than that of the HIG scan (90% versus 67%, $p < 0.001$). Thus, if focal infection is suspected, scintigraphy with ^{99m}Tc-labeled leukocytes is the preferable method. No cases exhibited a better imaging result with ^{99m}Tc-HIG scintigraphy than with ^{99m}Tc-labeled leukocytes.

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The observation that ^{67}Ga accumulates in neoplastic and inflammatory lesions (*1*) led to increasing interest in radionuclide methods to detect inflammation. However, because ^{67}Ga demonstrates poor specificity for infection (*2–6*), better methods were needed. In 1976, McAfee and Thakur (*7*) introduced ^{111}In-oxine for labeling leukocytes. Since then, ^{111}In-leukocyte imaging has become an established method for the detection of infectious and inflammatory lesions (*8–12*).

Recently, new radionuclear techniques have been introduced for evaluating infectious and inflammatory diseases. These include ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) labeled leukocytes (*6,13–15*), ^{99m}Tc-nanocolloid (*16,17*), ^{99m}Tc-labeled antigranulocyte antibodies (*18,19*) and, very recently, polyclonal human immunoglobulin G (HIG) labeled with ^{111}In (*20–25*) or ^{99m}Tc (*26–30*).

It is difficult to know which of these new methods is the most useful clinically. In this prospective study we compare the efficacy of ^{99m}Tc-HMPAO-labeled leukocytes and ^{99m}Tc-labeled IgG for detection of focal purulent disease or inflammatory reaction specifically caused by microbiologic agents and characterized by immigration of large numbers of leukocytes.

MATERIALS AND METHODS

Patients

Scintigraphy with ^{99m}Tc-HMPAO-labeled leukocytes and Technescan HIG was performed on 30 patients (15 male, 15 female, age range 26–85 yr, mean age 55 yr) with a known or strongly suspected focal infection. A total of 32 scintigraphies were performed with labeled leukocytes (two patients were examined twice) and 31 scintigraphies with labeled HIG (one patient examined twice). Sixteen patients were first imaged with ^{99m}Tc-labeled HIG and 14 patients were first imaged with ^{99m}Tc-labeled leukocytes. The interval between leukocyte and immunoglobulin imaging was at least 48 hr (range 2–4 days in 28 patients and 7 days in 2 patients). The study was approved by the Ethics Committee of the Clinic of Radiology, Helsinki University Hospital. Consent was obtained from the referring physician and the patient.

Patients were recruited from the departments of internal medicine and surgery. Eight were referred because of known or suspected wound infection. Six were known to have or were very strongly suspected of having an abdominal or pelvic abscess. Four were suspected of having prosthetic vascular graft infections. The remaining four had fever of unknown origin (FUO) with an increased serum concentration of C-reactive protein, a raised erythrocyte sedimentation rate and leukocytosis. Three were referred because of suspected bone infection, two for suspected spondylitis and two had suspected spleen abscess. One patient with active Crohn's disease in whom an abdominal abscess was suspected, was imaged because of an unfavorable response to steroid and antimicrobic therapy.

Of these 30 patients, 19 had focal purulent disease confirmed by one or more of the following: bacteriologic culture, microscopic examination of a biopsy, computed tomography (CT), ultrasonography (US), magnetic resonanse imaging (MRI), conventional ra-

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diography, skeletal scintigraphy, endoscopy, laboratory tests (above) and other clinical data compatible with the favorable response of an infection to antimicrobic therapy. The same procedures and clinical follow-up were used in the other 11 patients to exclude focal infection.

Radiopharmaceuticals

Leukocyte Labeling with ^{99m}Tc-HMPAO. Mixed leukocytes were isolated and labeled with freshly prepared ^{99m}Tc-HMPAO as described previously (*6*). Forty milliliters of venous blood was drawn into a 60-ml plastic syringe containing 10 ml of acid citrate dextrose and 10 ml of 6% hydroxyethyl starch to accelerate the sedimentation. The erythrocytes were allowed to settle at room temperature for 1 hr. The supernatant was centrifuged in sterile tubes at 100 g for 5 min. The platelet-rich supernatant was then separated and centrifuged at 2000 g for 5 min to obtain cell-free plasma. White blood cells were suspended in 1 ml of cell-free autologous plasma. Technetium-99m-HMPAO was generated by adding 600 MBq of ^{99m}Tc in 6 ml of isotonic saline to a vial containing HMPAO (Ceretec, Amersham International, U.K.). Five milliliters (500 MBq) of ^{99m}Tc-HMPAO-complex was added to the leukocyte suspension which was allowed to incubate for 10 min at room temperature. The cell suspension was centrifuged at 100 g for 5 min. The supernatant was discarded and the cells resuspended in 5 ml of cell-free plasma and reinjected intravenously. The mean injected dose was 260 MBq and the average labeling efficiency of leukocytes was 47% (range 28%–72%). Time required for the labeling procedure averaged 1.5 hr.

Preparation of ^{99m}Tc-HIG. Labeling of HIG (Technescan HIG, Mallinckrodt Diagnostica, Petten, The Netherlands) was performed according to manufacturer's instructions by aseptically adding about 555 MBq pertechnetate in a volume of 0.5 ml to a vial containing 1 mg of polyclonal human IgG, 4.2 mg of disodium tartrate and 8 μg of stannous cloride. The solution was left to incubate for 20 min at room temperature, after the vials in which it was contained were shaken gently a few times. As determined by gel filtration, the labeling yield was always over 97%. A mean dose of 300 MBq was injected in the patient.

Imaging

Planar images were obtained 0.5 hr, 2 hr, 4–6 hr and 24 hr after the injection of labeled leukocytes or HIG. A gamma camera with a large field-of-view (Maxi camera 400 T, General Electric, Copenhagen, Denmark or Rota camera ZLC 75, Siemens, Uithoorn, the Netherlands) was used, connected to a computer and equipped with a low-energy, high-resolution collimator. At least one anterior whole-body image and spot images of any suspected areas in two projections were obtained.

Analysis of Scintigrams

The scintigrams were analyzed by two nuclear physicians who were blind to the clinical information and two radiologists who were aware of the clinical history or other diagnostic procedures if available. On rare occasions when readings differed, the final decision was made by consensus. A blind analysis was not, however, necessary for the purpose of this study, which was a comparison of the capacity of the two tracers to demonstrate focal purulent lesions. Findings in the scintigraphies were classified according to visualization of uptake of lesions by both methods in three grades: 0 = not detectable; + = detectable; and ++ = readily detectable. Background activity served as a reference standard. A focal lack of activity was defined as a cold lesion (cl).

When the pathologic uptake was caused by an infectious process or purulent inflammation confirmed by the diagnostic procedures mentioned earlier, the scintigram was considered to be a "true-positive." A positive scintigram was considered "false-positive" when, by other diagnostic modalities, the finding was verified to be noninfectious or nonpurulent. A negative scintigram was considered to be "true-negative" when no focal infection was found and "false-negative" when a focal infectious process was found by other diagnostic procedures. Cold lesions were considered "false-negative" because of their nonspecificity.

RESULTS

Whole-body distribution of ^{99m}Tc-HMPAO-labeled leukocytes differed from distribution of ^{99m}Tc-HIG. Normal distribution of the activity of the ^{99m}Tc-leukocyte scan has been described in detail previously (*13–15*). In the present study, at 2–4 hr after administration of labeled leukocytes, lung, heart, iliac vein and kidney activity was minimal, whereas liver and bone marrow activity was moderate and spleen activity strong. At 2–4 hr after injection of ^{99m}Tc-HIG, bone marrow uptake was very small and spleen uptake slight, whereas uptake in liver, kidney, heart and iliac vein was marked. This corresponds to previous findings (*28–30*). The urinary bladder was visualized by both agents. After 4–6 hr, the bowel was always visualized with labeled leukocytes but not with HIG.

Results of imaging with labeled leukocytes and HIG are summarized in Tables 1 and 2. Of the eight patients suspected of having a wound infection, five had a true-positive and three a true-negative scintigram with both agents.

Six patients were referred for these studies because of known or suspected abdominal or pelvic abscess. The ^{99m}Tc-leukocyte scan revealed three true-positive and three true-negative cases, whereas ^{99m}Tc-HIG yielded two false-negative foci (Fig. 1) and showed three true-negative and only one true-positive finding.

All prosthetic vascular graft infections were imaged with labeled leukocytes as true-positive. In two patients, HIG-scintigraphy was falsely negative. In one of these patients, a follow-up study with both agents was made after treatment of 2 mo, and the leukocyte scan still showed focal uptake, albeit less than in the initial study, which was in accordance with the clinical findings. HIG scintigraphy was negative also on follow-up.

All patients with fever of unknown origin were imaged because of suspected focal infectious processes. One of these patients had intercurrently autoimmune hemolytic anemia and had a strong accumulation of leukocytes in the upper parts of both lungs, which was also the case in the follow-up study. HIG scintigraphy was negative with this patient, both initially and in follow-up. The patient died and pulmonary infection was verified on autopsy. Three patients with FUO (one with myeloma and two with chronic lymphatic leukemia) showed true-negative findings with both methods.

Two patients with acute osteomyelitis had increased uptake of tracer with both methods, although uptake was weaker with HIG. One female HLA-B27-positive patient

TABLE 1
Imaging with ^{99m}Tc-HMPAO-Labeled Leukocytes and Technescan HIG

Known or clinical suspicion of focal infection	n	^{99m}Tc leukocytes				^{99m}Tc HIG			
		TP	FP	TN	FN	TP	FP	TN	FN
Wound infection	8	5	—	3	—	5	—	3	—
Abdominal or pelvic abscess	6	3	—	3	—	1	—	3	2
Prosthetic vascular graft infection	4	4	—	—	—	2	—	—	2
FUO	4	1	—	3	—	—	—	3	1
Osteitis	3	2	—	1	—	2	1	—	—
Spondylitis	2	—	—	1	1 (cl)	—	1	—	1
Spleen abscess	2	—	—	—	2 (cl)	—	—	—	2 (cl)
Crohn's disease/abdominal abscess	1	1	—	—	—	1	—	—	—
Total	30	16	—	11	3 (3/3 cl)	11	2	9	8 (2/8 cl)

TP = true-positive; FP = false-positive; TN = true-negative; FN = false-negative; and cl = cold lesion.

had pain and edema in the right ankle in connection with *Serratia marcescens-sepsis*. There was pathologic uptake of HIG in the right calcaneus and subtalar joint. Scintigraphy with labeled leukocytes was normal and low-field MRI showed no pathologic changes. An aspiration sample from the subtalar joint was sterile. The patient was treated under a diagnosis of reactive osteitis and arthritis.

A paraplegic patient with suspected spondylitis in the lower thoracic spine had surgery for ependymoma at the 2–5 thoracic vertebrae; exploration was also made at T10–12. An increased signal intensity on T_2-weighted MR images occurred in the vertebrae involved, T11–L1 and disc spaces. Scintigraphy with ^{99m}Tc-HMPAO leukocytes was normal, and there was diffuse accumulation of ^{99m}Tc-HIG at the lower thoracic spine and paravertebral region. Aspiration was performed twice and yielded sterile fluid; an open biopsy showed only granulation. The other patient with suspected spondylitis had an increased signal intensity on T_2-weighted MR images in the L3 vertebral body and a suspected paravertebral abscess at the same level. The ^{99m}Tc-HIG scintigram was normal, while ^{99m}Tc-HMPAO labeled leukocytes showed a cold lesion in the L3 vertebral body and no accumulation of tracer in the paravertebral region (Fig. 2). Aspiration from the paravertebral abscess showed marked leukocytosis; *Mycobacterium tuberculosis* was cultured from the sample.

TABLE 2
Sensitivity, Specificity, Accuracy and Predictive Values of ^{99m}Tc-HMPAO-Leukocyte and Technescan HIG Scintigrams in Detection of Focal Purulent Disease

	^{99m}Tc leukocyte	^{99m}Tc HIG
Sensitivity (%)	84 (16 TP, 3 FN)	58 (11 TP, 8 FN)
Specificity (%)	100 (11 TN, 0 FP)	82 (9 TN, 2 FP)
Accuracy (%)	90	67
Positive predictive value (%)	100	85
Negative predictive value (%)	79	53

TP = true-positive; FP = false-positive; TN = true-negative; and FN = false-negative.

Two bacteriologically verified splenic abscesses appeared as cold lesions with both agents. Because of strong normal activity of the spleen at 2 hr, the defect was better delineated by labeled leukocytes than by labeled HIG (Fig. 3). Findings by both methods were considered nonspecific and, hence, false-negative.

A patient with symptomatic Crohn's disease was imaged because of unfavorable response to steroid and antimicrobic therapy; an abdominal abscess was suspected but could not be confirmed. This patient had what could be regarded as "purulent" Crohn's disease: endoscopy showed active disease in the cecum, the ascending colon and the proximal part of the transverse colon. Histopathologically there was a strong leukocyte infiltration in the lamina propria extending beneath the muscularis mucosa. Although the finding was positive with both agents, the tracer activity from ^{99m}Tc-HMPAO-labeled leukocytes was much stronger in the diseased area than it was with ^{99m}Tc-HIG. The leukocyte image also delineated affected areas in more detail than did ^{99m}Tc-HIG, which showed only a faint accumulation in the ascending colon.

The final diagnoses and scintigraphic findings for all lesions are presented in Table 3. Of 19 verified cases, 13 were readily detectable with leukocyte scintigraphy, whereas there were no such cases with Technescan HIG scintigraphy. The methods were equally effective on three patients and in no instances was ^{99m}Tc-HIG better than ^{99m}Tc-HMPAO-leukocytes. The sensitivity and specificity of the ^{99m}Tc-HMPAO leukocyte scan were 84% and 100%, respectively, and 58% and 82%, respectively, for the ^{99m}Tc-HIG scan. The difference in accuracy between the ^{99m}Tc-leukocyte scan and ^{99m}Tc-HIG scan was statistically significant (90% versus 67%, $p < 0.001$, by the chi-square

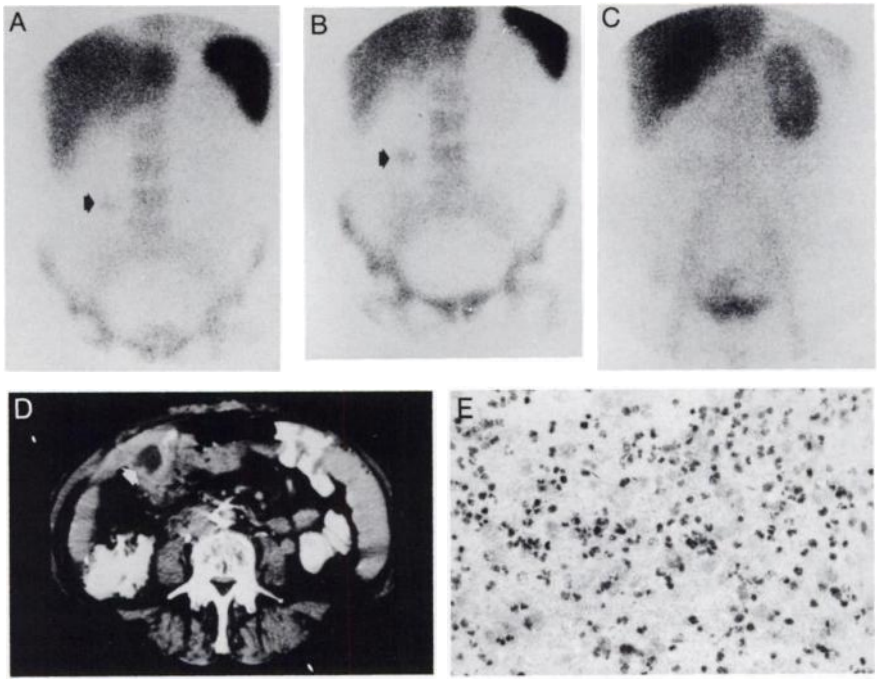

FIGURE 1. Anterior images of abdomen in patient with postoperative abdominal abscess. (A) ^{99m}Tc leukocyte scan at 2 hr and (B) at 4 hr showing increasing uptake of tracer on right side of abdomen. (C) ^{99m}Tc-HIG image at 24 hr showing no pathologic uptake. (D) CT scan confirming the presence of abscess under stomach wall. (E) Aspiration sample from abscess (May–Grünwald–Giemsa stain, magnification 200×) showing accumulation of white blood cells. Arrows indicate corresponding foci.

test with Yates correction). The positive and negative predictive values of leukocyte imaging were 100% and 79%, respectively, and 85% and 53%, respectively, for HIG imaging.

DISCUSSION

Technetium-99m-HMPAO radiolabeling of leukocytes in vitro was first described in 1986 (*13*) after which good results of its clinical use for identifying infectious and inflammatory lesions are documented (*14,15,31–33*). The ^{99m}Tc-HMPAO leukocyte method has advantages over ^{111}In-oxine with respect to image quality, acquisition time and radiation dose to the patient. The nonspecific bowel accumulation of ^{99m}Tc-HMPAO leukocytes at 4 hr and 24 hr after injection generated controversy on its suitability for abdominal imaging (*34,35*). However, a recent study by Lantto et al. (*36*) showed that nonspecific bowel accumulation was never present when images were obtained less than 2 hr after injection of ^{99m}Tc-HMPAO-labeled leukocytes.

Radioimmune detection of tumors suggests that this method could be also used for detecting focal infections (*37–39*). In an experimental study, Rubin et al. (*20*) showed that specific immune imaging of microbial processes is possible; in their work, nonspecific IgG also localized at the site of infection. Following those findings, promising results have been reported with ^{111}In-labeled human nonspecific immunoglobulin G (*21–25*). Because ^{111}In has a longish half-life of 67.4 hr and gives a relatively high radiation dose to the patient, ^{99m}Tc was used for labeling immunoglobulins. In initial studies, ^{99m}Tc-labeled nonspecific polyclonal human immunoglobulin G (HIG) was seen to be effective for detecting infections in different tissues (*26,27*). In addition, the technetium complex has several advantages over leukocyte scintigraphy: (1) only a one-step kit formulation is needed; (2) the labeling procedure is simple;

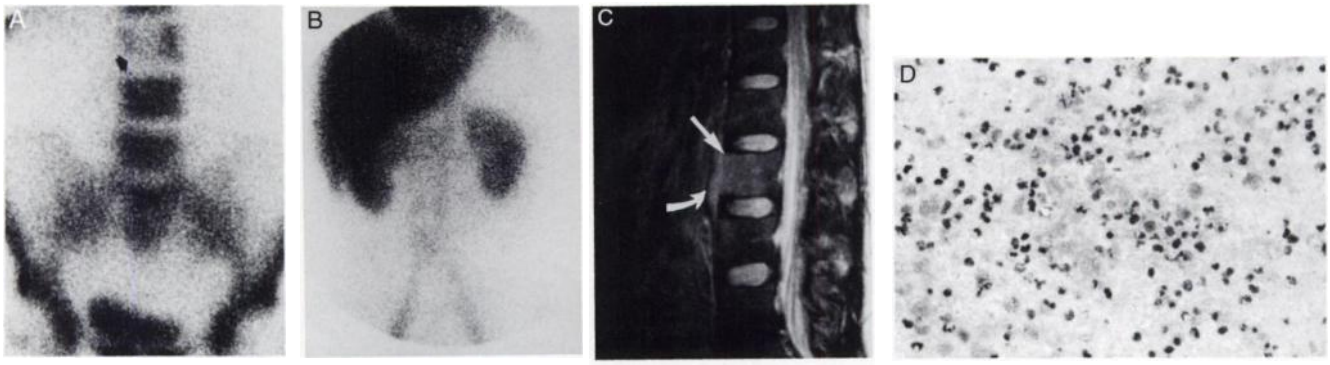

FIGURE 2. (A) Spondylitis in L3 vertebral body and paravertebral abscess, with ^{99m}Tc leukocyte scan at 4 hr showing focal defect (arrow) in L3 vertebral body. (B) ^{99m}Tc-HIG scan at 5 hr interpreted as normal. (C) T_2-weighted MRI showing increased signal intensity in L3 vertebral body (arrow) and prevertebral abscess (curved arrow) in sagittal plane. (D) Aspiration from abscess showing many leukocytes (May–Grünvald–Giemsa stain, magnification 200×). *M. tuberculosis* cultured from sample.

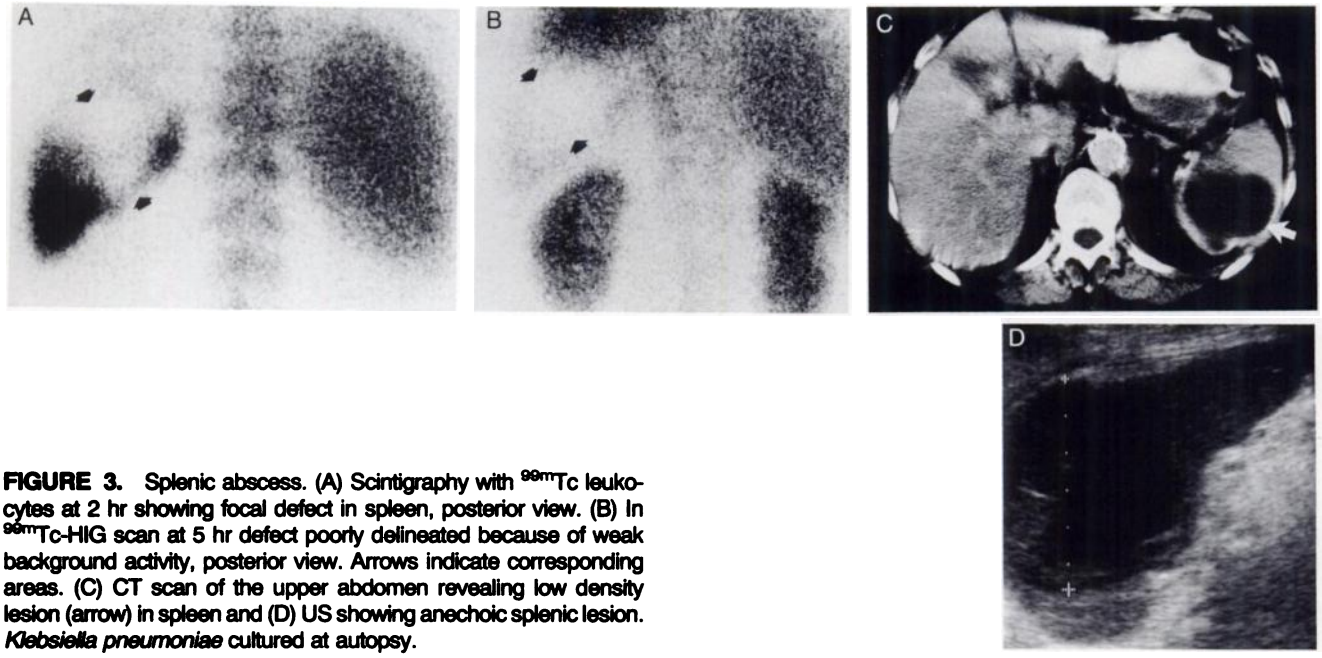

FIGURE 3. Splenic abscess. (A) Scintigraphy with ^{99m}Tc leukocytes at 2 hr showing focal defect in spleen, posterior view. (B) In ^{99m}Tc-HIG scan at 5 hr defect poorly delineated because of weak background activity, posterior view. Arrows indicate corresponding areas. (C) CT scan of the upper abdomen revealing low density lesion (arrow) in spleen and (D) US showing anechoic splenic lesion. *Klebsiella pneumoniae* cultured at autopsy.

and (3) the radiopharmaceutical may be injected without cell separation.

Antibodies can be labeled with ^{99m}Tc either directly or indirectly (*40–43*). Both methods have been used successfully in clinical trials (*44,45*). In a recent work, Hnatowich et al. (*46*) demonstrated in vitro and in vivo, in mice, important differences in ^{99m}Tc-labeled IgG antibodies prepared by the different methods. When compared with an indirect method, ^{99m}Tc was unstable toward transchelation in one direct method. This instability influenced biodistributions in mice and may influence the quality of images in clinical practice. In the present study we used Technescan HIG, in which IgG is directly labeled with ^{99m}Tc.

Technetium-99m-labeled HIG has been compared with ^{111}In leukocytes in evaluation of inflammatory bowel diseases (*28*) and with ^{99m}Tc monoclonal antibodies for detection of chronic osteomyelitis (*29*). In the present study, scintigraphy with labeled leukocytes was clearly superior to labeled immunoglobulin (Table 3). Significantly more lesions were visualized by leukocytes than by HIG (Tables 1 and 2). The faster blood clearance of the leukocytes results in lower background activity and an improved lesion-to-background ratio. In addition, the lesions were much better delineated with leukocytes (Fig. 4) and became visible much sooner, often within a few minutes after injection of labeled leukocytes. The visualization was slower with HIG than with labeled leukocytes and uptake into the lesion weaker.

Arndt et al. (*30*) compared directly-labeled HIG and ^{111}In-granulocytes for detecting activity of intestinal segments involved in a group of 14 patients with inflammatory bowel disease (IBD). They concluded that in patients with

TABLE 3
Comparison of ^{99m}Tc-Labeled Leukocytes with Technescan HIG: Final Diagnoses and Scintigraphic Findings

		^{99m}Tc leukocyte			^{99m}Tc HIG		
Focal purulent disease	n	0	+	++	0	+	++
Wound infection	5	—	1	4	—	5	—
Abdominal or pelvic abscess	3	—	—	3	2	1	—
Prosthetic vascular graft infection	4	—	2	2	2	2	—
Osteitis	2	—	—	2	—	2	—
Spondylitis with paravertebral abscess	1	1 (cl)	—	—	1	—	—
Pulmonary infection	1	—	—	1	1	—	—
Spleen abscess	2	2 (cl)	—	—	2 (cl)	—	—
Crohn's disease	1	—	—	1	—	1	—
Total	19	3 (3/3 cl)	3	13	8 (2/8 cl)	11	—

0 = not detectable; + = detectable; ++ = readily detectable; and cl = cold lesion.

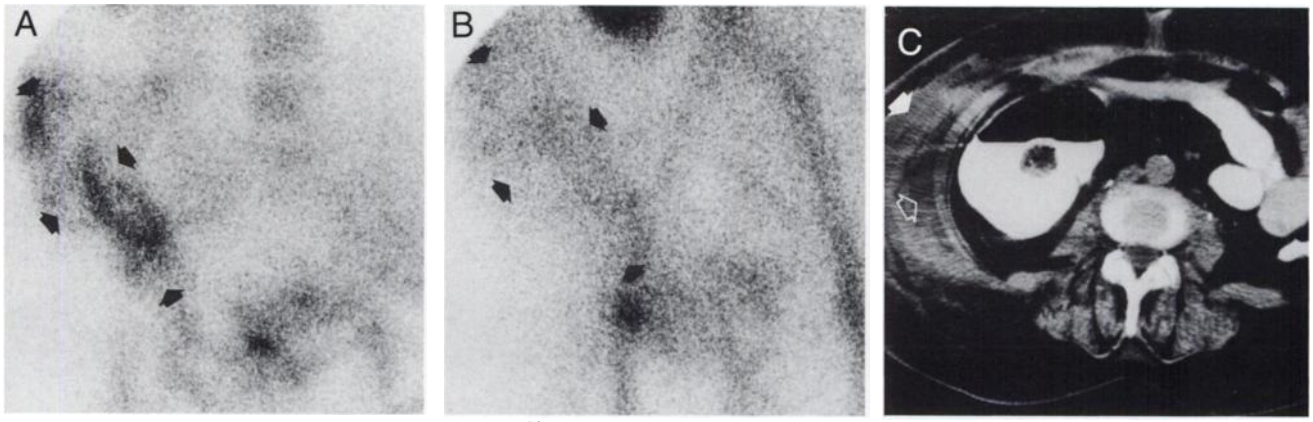

FIGURE 4. Postoperative cellulitis and abscess. (A) ^{99m}Tc leukocyte scan at 4 hr showing stronger accumulation of tracer; lesion better delineated than in ^{99m}Tc-HIG scan at 5 hr (B). Arrows indicating the corresponding areas. (C) CT scan revealing edema (closed arrow) and a small collection of fluid (open arrow) in the abdominal wall.

active IBD, ^{99m}Tc-HIG did not demonstrate diseased intestinal segments with sufficient sensitivity mainly because of increased background activity throughout the entire abdomen from 6 hr to 24 hr. There also appeared to be some physiological activity in the colon. Although we could not identify nonspecific activity in the bowel, unlike findings of Arndt et al. (*30*), the ^{99m}Tc-HIG scintigram in our patient with Crohn's disease was much inferior to the scintigram with ^{99m}Tc-labeled leukocytes. In a leukocyte study, bowel activity is not a problem if serial imaging of the abdomen is performed during the first 2 hr after injection (*36*).

Some cases in our study are worthy of comment. One patient with spondylitis and a paravertebral abscess caused by *M. tuberculosis* showed neither increased uptake of the tracer or cold lesion with HIG scintigraphy. The affected L3 vertebral body was cold in the leukocyte scan and no accumulation of labeled leukocytes occurred in the paravertebral abscess, which is surprising because the patient had large numbers of leukocytes in the paravertebral abscess. Obviously, leukocytes that migrated to the paravertebral tuberculous abscess originated from some other leukocyte pool than that of the injected leukocytes. Such a source of leukocytes is obviously the bone marrow which may generate young neutrophils preferentially accumulating in the abscess.

Liver and spleen abscesses can be problematic in scintigraphic studies because of moderate or strong physiological activity in these organs. In our series, for two patients with bacteriologically verified spleen abscesses, both agents showed a focal defect. This was due to strong background activity of the normal spleen tissue.

There were two false-positive HIG scintigrams. One patient with spondylitis showed diffusely increased activity in the lower thoracic spine. Aspiration samples were sterile and histopathologic examination did not confirm infection. The other patient (HLA-B27+) with a positive HIG scintigram showed increased activity in the right subtalar joint and calcaneus. Here also, the aspiration sample was sterile and the leukocyte scan was negative.

In conclusion, scintigraphy with ^{99m}Tc-HMPAO-labeled leukocytes is the preferable method for detection of focal purulent disease. In our series of 30 patients, there was no case that had a better imaging result with ^{99m}Tc-HIG scintigraphy than with ^{99m}Tc-labeled leukocytes. We do not recommend use of directly-labeled HIG as the primary scintigraphic method when focal purulent disease is suspected. It could be argued that scintigraphy with ^{99m}Tc-HIG might be useful in evaluating nonpurulent inflammations and reactive arthropathies, but this needs further investigation. Promising results have already been reported for measuring synovial inflammation with directly labeled HIG in rheumatoid arthritis (*47–49*). We point out that conclusions from our results with Technescan HIG cannot be generalized to other ^{99m}Tc-IgGs, because others have shown (*46*) that the labeling method of ^{99m}Tc-IgG can influence the utility of these radiopharmaceuticals.

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