

LeukoScan for Imaging Infection in Different Clinical Settings

A Retrospective Evaluation and Extended Review of the Literature

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Purpose: The aim of the current study was to determine the overall diagnostic accuracy of Tc-99m-labeled anti-granulocyte monoclonal antibody Fab' fragments (LeukoScan) for the routine detection of bone and soft tissue infections in a retrospective evaluation.

Patients and Methods: 138 patients (63 men, 75 women; mean age, 58.29 ± 25.38 years) with fever of unknown origin and possible endocarditis (n = 59), infection of arthroplastic joints (n = 20), arthritis (n = 16), peripheral (n = 15) and central bone infections (n = 14), soft tissue infection (n = 6), appendicitis (n = 4), pericarditis (n = 2), or vascular graft infection (n = 2) underwent imaging after injection of 555 to 925 MBq (15 to 25 mCi) Tc-99m-labeled anti-granulocyte monoclonal antibody Fab' fragments (LeukoScan).

Results: True-positive results were found in 63 of 81 lesions. The overall sensitivity and specificity were 76% and 84%, respectively. In arthritis, seven of seven foci could be detected, whereas false-negative results were found in infections of the femoral bone in three of nine lesions and in periprosthetic infections of long bones in three of eight lesions. Good results were found in five of six soft-tissue infections, in four of six patients with endocarditis, in three of four atypical cases of appendicitis, in two of two infected vascular grafts, and in one of one patient with pericarditis. Subacute and chronic infections of the spine always showed photopenic areas in eight of eight patients. If photopenic lesions were included as diagnostic criteria, the sensitivity and specificity were 88% and 67%, respectively.

Conclusions: Tc-99m-labeled anti-granulocyte monoclonal antibody Fab' fragments can be used for imaging acute infections of peripheral bones and soft tissues. False-negative results are likely in patients with chronic infections. Sensitivity can be increased while decreasing

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specificity by including photopenic lesions in the spine as diagnostic criteria for localizing disease.

Key Words: Diagnostic Imaging, Fab' Fragments, Infections.

TO DATE, THE gold standard for nuclear medicine imaging of infection has been the use of radiolabeled autologous leukocytes (1–3). This requires ex vivo handling of blood, time-consuming techniques, and special training, and it puts laboratory personnel and patients at risk for infection (4). However, several other methods can overcome these problems. Intact murine antibodies are easy to handle and show rapid results with high sensitivity and specificity (5–11). The major disadvantage of using intact murine antibodies is the development of human antimouse antibodies (12,13) and associated allergic reactions. The human antimouse antibody response can be addressed in several ways. The first is to administer human or humanized antibodies (14,15). A disadvantage of these antibodies is their low degree of specificity, because a correct differentiation between specific uptake in an infectious focus and nonspecific accumulation in an inflamed lesion often is impossible. The second option is to use fragments of antibodies rather than intact immunoglobulin G (16). Several multicenter studies have used Tc-99m-labeled monoclonal antibody fragments (Tc-99m Fab' fragment) to image infection in “preselected” groups of patients with bone and soft-tissue infections. They found a high degree of sensitivity and specificity in this particular patient pop-

Received for publication May 22, 2002. Revision accepted November 25, 2002.

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DOI: 10.1097/01.RLU.0000057613.86093.73

ulation (17,18). Because of the smaller size of the Fab' fragment of only 50 kd, rapid imaging is possible 1 to 4 hours after injection. This is due to the rapid uptake into the lesion and a lower degree of background activity, resulting in excellent imaging quality (16).

In "mixed" patient populations without sufficient clinical signs and symptoms to establish a diagnosis, there is an increasing demand for novel imaging methods. Ideally, these should have no adverse effects for patients, because repeated imaging is frequently necessary. In this particular group of patients, the only data available are for whole murine monoclonal antibodies (5,6,8,9,19,20). In preselected patients, Tc-99m Fab' fragment imaging was previously proved to be an easy-to-handle antibody, with high sensitivity and specificity for targeting infectious lesions and without adverse effects (17,18). The aim of the current retrospective study, therefore, was to evaluate Tc-99m Fab' fragment scanning in a mixed patient population for whom labeled leukocytes and complete antibodies are well accepted for imaging infection (8,9,19-21).

Patients and Methods

For this study, 138 patients (mean age, 58.29 ± 25.38 years; 63 men, 75 women) referred to the nuclear medicine department with either fever of unknown origin and possible endocarditis or bone or soft tissue infection were examined. In patients with fever of unknown origin and possible endocarditis, two or more of the revised Duke criteria (22) were present. Major criteria included positive findings for blood culture, for cardiac echogram, and a valvular prolapse. Minor criteria were rectal temperature higher than 38.3°C for at least 2 weeks or more, and immunologic or vascular alterations. In patients with possible bone or soft tissue infection, one or more of the following criteria were present: clinical signs of osteomyelitis (local edema, warmth, and local erythema) and two or more blood cultures positive for the same organism. In this group of patients, ultrasound, computed tomography, magnetic resonance imaging, and conventional radiography were used as reference imaging procedures to make the final diagnosis. In-111 oxine or Tc-99m HMPAO-labeled leukocytes were used to compare the nuclear medicine techniques.

Echocardiography

In all patients with fever of unknown origin and possible endocarditis, transthoracic echocardiography was performed using two-dimensional, M-mode, Doppler, and color-flow Doppler techniques in standard views. Studies were performed using Hewlett-Packard Sonos 1,000 and 1,500 ultrasound imaging systems with a 2.5-MHz transducer (Hewlett-Packard Co. Medical Products Group, Carpinteria, CA). If no vegetation was detected on transthoracic examination, transesophageal echocardiography was performed using a single-plane 5-MHz probe with color flow Doppler function (Hewlett-Packard 21362 A/C) on the same or the following day. The examinations were interpreted when they were performed by a physician experienced in echocardiography and documented on videotape for review by a second physician. Echocardiog-

raphy was considered positive if vegetations, new valvular dysfunction, or perivalvular abscess could be demonstrated using either approach. Less specific signs of endocarditis, such as inconclusive valvular attachments that could either represent vegetations or sclerotic or myxomatous lesions, were considered negative findings.

Fever of Unknown Origin

Fever of unknown origin was defined as a rectal temperature of 38.3°C for at least 2 weeks in patients hospitalized for longer than 1 week (23). These patients had full biochemical and hematologic laboratory workups that failed to establish a diagnosis. Appropriate radiographic investigations, including a chest radiograph, were also required.

Monoclonal Antibody Preparation and Labeling

LeukoScan (Sulesomab) is a Tc-99m-labeled Fab' fragment of IMMUN-MN3, an immunoglobulin G1 murine monoclonal antibody produced from a hybridoma developed by fusion of murine myeloma (SP 2/0) cells with spleen lymphocytes obtained from a mouse immunized with carcinoembryonic antigen. The antibody reacts strongly with nonspecific cross-reacting antigen 90 ($K_a = 0.5 \times 10^8 \pm 0.2 \times 10^8 \text{ l/mol}$) present on human granulocytes (24,25). The Fab' fragment was provided in a ready-to-label lyophilized kit from Immunomedics (Morris Plains, NJ). The Fab' fragment was labeled by adding 1,000 to 1,500 MBq (27 to 40 mCi) Tc-99m pertechnetate in isotonic saline solution directly into the vial containing 0.3 mg of the monoclonal antibody Fab' fragment and shaking sporadically for 5 minutes. When the radiolabeling was performed exactly in this way, previous studies have found less than 1% of free technetium in the labeled product (17). For patient imaging, approximately 0.25 mg LeukoScan labeled with $1,110 \pm 185$ MBq (30 ± 5 mCi) Tc-99m sodium pertechnetate was diluted with saline and injected intravenously. Patients having planar whole-body scintigraphy or single spot views received a dose of 555 ± 111 MBq (15 ± 3 mCi) and an increased dose of 925 ± 185 MBq (25 ± 5 mCi) for SPECT.

Imaging

Whole-body images were obtained 1, 4, and 24 hours after injection using a dual-head gamma camera (Prism 2000; Picker, Cleveland, OH) with parallel-hole, high-resolution, low-energy collimators using the 140-keV Tc-99m peak, a 256×256 matrix, and a preselected time of 25 minutes/image. For planar regional scans of the region of interest (head, neck, chest, abdomen, pelvis, and bone), a single-head gamma camera (Picker SX 100) was used 1, 4, and 24 hours after injection. The same imaging conditions for differentiating osteomyelitis from soft-tissue infection in anterior, posterior, and oblique projections was applied. SPECT images in patients with suspected endocarditis was performed 17 to 26 hours after injection using a triple-head gamma camera (Prism 2000) with a 128×128 matrix; 25 minutes/image; 30 images; 120° angle; parallel-hole, high-resolution, low-energy collimators using the 140-keV Tc-99m peak. For SPECT reconstruction, an iterative algorithm was applied (26).

Biodistribution and Target:Background Ratio

For 10 patients, the distribution of tracer in the liver, spleen, kidneys, bone marrow, and infectious lesion was measured and

compared with healthy contralateral, and whole-body uptake of the radiolabeled monoclonal antibody Fab' fragment. The kinetic considerations included whole-body imaging performed 1, 4, and 24 hours after injection.

Bowel Uptake

The distribution of radioactivity in the abdomen was examined visually in 10 patients 10, 15, 20, 30, 40, 50, and 60 minutes and 3, 4, and 24 hours after injection.

Statistics

Imaging sensitivity, specificity, positive predictive and negative predictive values, and diagnostic accuracy were calculated according to the usual formulas. Data were expressed as mean values with standard deviations (\pm SD). Findings of *in vitro* laboratory tests were analyzed for significant differences using the paired Student's *t* test.

Results

Characteristics of the Fever of Unknown Origin and Possible Endocarditis Group

Of 59 patients with fever of unknown origin, 6 had subacute infective endocarditis (10%). On admission, all 59 patients had fever and an elevated erythrocyte sedimentation rate. All patients had received antibiotics for more than 10 days before scintigraphic imaging. Most of these patients (51 of 59, or 86%) had leukocytosis, or a left shift in the differentiated complete blood count. In the group of patients in whom the diagnosis of endocarditis was made, the pathogenic microorganism could be isolated in five of six patients, whereas 1 patient had a negative blood culture. Five of the six patients (83%) had mechanical prosthetic valves: three had aortic valve prostheses, one had a mitral valve prosthesis, and one had a combined aortic/mitral valve prosthesis. In 53 of 59 (90%) patients, endocarditis could not be diagnosed using these criteria. Immunoscintigraphy with Tc-99m Fab' fragments (LeukoScan) showed significant tracer uptake in four of the six studies from patients with subacute endocarditis (Fig. 1), yielding a sensitivity of 66%. Tracer accumulation was observed projecting to the valvular plane, ventricular outflow tracts, and adjacent endocardium. However, tracer uptake could not be assigned to a distinct cardiac valve.

Immunoscintigraphy was negative in 42 of the 53 patients without endocarditis (true negatives), yielding a specificity of 79%. Results of radioimaging were false positive in 11 patients (Tables 1 and 2). In five of these patients, increased blood-pool activity could be one of the possible explanations for false-positive imaging, because SPECT was performed 17 to 19 hours after injection in these particular patients. In the remaining patients, no convincing explanation could be found for tracer accumulation projecting to the heart. Because of

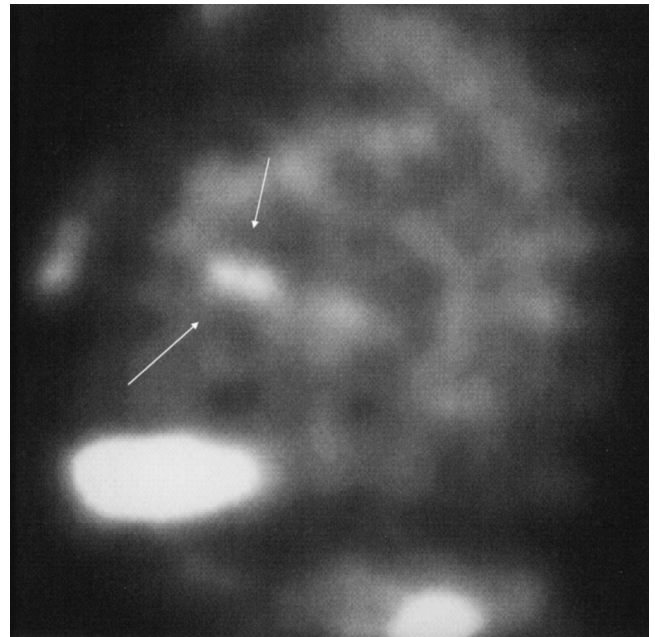


Fig. 1. A 56-year-old patient had endocarditis of the mechanical aortic prosthetic valve.

residual blood-pool activity on tomographic scans, only the images obtained 24 to 26 hours after injection could be evaluated accurately. Follow-up studies were performed in two of the four patients with a true-positive scintigraphic diagnosis of endocarditis. In both patients, the findings of immunoscintigraphy became negative with clinical improvement, whereas the vegetations persisted and the results of echocardiography remained positive.

Characteristics of the Prosthesis and Bone-Joint Group

In this group, 71 patients were examined. The patient data and final diagnoses were obtained by histologic analysis ($n = 22$), biopsy ($n = 15$), and clinical follow-up ($n = 71$). As imaging methods, the results of In-111 oxine ($n = 11$) and Tc-99m HMPAO ($n = 9$) labeled leukocyte scans, three-phase bone scintigraphy ($n = 11$), planar radiography ($n = 27$), magnetic resonance imaging ($n = 9$), and computed tomography ($n = 16$) were available. Seventy-eight different potential infectious or inflammatory sites were evaluated in the 71 patients. In 20 patients with possible infection of arthroplastic joints (knee arthroplasty [$n = 13$] and hip arthroplasty [$n = 7$]), eight sites were indicated by pathologic findings or other correlative methods. Tc-99m Fab' fragment scintigraphy identified 5 of them as true positive, 11 as true negative, 3 as false negative, and 1 as false positive. The three false-negative sites were correctly detected by In-111- or Tc-99m HMPAO-labeled leukocytes. False-pos-

TABLE 1. Immunoscintigraphy in Patients with Possible Endocarditis

Patient	Age (years)	Sex	Fever (weeks)	ESR (mm/h)	Leukocyte Count/mm ³	Isolated Microorganism	TTE-TEE	Localization	LeukoScan
1	68	M	7	68	11,300	<i>S. pneum.</i>	+/+.....+/+/+	Aortic (m)	+
2	56	F	6	45	9,800	None	+/+/+ -	Aortic (n)	-
3	54	F	11	36	8,800	<i>S. aureus</i>	+/-/- +/+/+	Aortic (m)	+
4	62	F	5	—	12,250	<i>Pseudomonas</i>	+/+/- -	Mitralic (m)	+
5	78	M	12	72	13,200	<i>S. viridans</i>	+/-/- +/+/+	Comb. (m)	+
6	62	F	13	52	—	<i>S. Epiderm</i>	+/-/- +/+/+	Mitralic (m)	-
Mean	63.33		9.00	54.60	11,070.00				
x ± SD	8.73		3.40	15.22	1,785.21				

Normal values: WBC, 4.0–11.0 × 1189⁹/l; ESR, <15 mm/h.

ESR, erythrocyte sedimentation rate; WBC, white blood cell count (leukocytes); TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; Strep., streptococcus; Staph., staphylococcus; Pneum., pneumoniae; Epiderm., epidermidis; (m), mechanical prosthetic valve; (n), natural valve; +/+/+ or -/-/- presence or absence of vegetations/new valvular dysfunction/perivalvular abscess.

itive uptake was seen several days after knee injury in a post-traumatic hemarthrosis. Conversely, Tc-99m Fab' fragment imaging correctly excluded a possible infection of a prosthetic shaft. In 16 patients with suspected arthritis, 7 sites were confirmed by Tc-99m Fab' fragment scanning. The Tc-99m Fab' fragment scanning recognized all 7 as true positive (arthritis = 2, synovitis = 5). In 29 patients with possible infections of appendicular (n = 21) and axial bones (n = 8), 17 sites were confirmed. In the case of appendicular bone infections, the Tc-99m Fab' fragment detected 6 as true positive, 10 as true negative, 2 as false positive, and 3 as false negative. False-positive findings were seen in patients with advanced periarticular calcification (1 hip joint, 1 knee joint), which may be irritating to the soft tissues, resulting in granulocyte migration. False-negative results were seen mostly in patients with post-traumatic diaphyseal long-bone infections and localized osteomyelitis in the bone shaft. In patients with infections of the axial bones (n = 8), Tc-99m Fab' fragment scanning detected 8 as false negative and none as true positive. In this patient group, however, magnetic resonance imaging was the

only diagnostic procedure available as a reference, in some cases combined with three-phase bone scans (Table 3). Table 4 summarizes the statistical findings.

Characteristics of the Soft Tissue/Appendix and Vascular Groups

Six patients with possible soft tissue infection were examined. Tc-99m Fab' fragment scanning recognized five as true positive (subdiaphragmatic abscess = one, skin infection = one, soft tissue fistula = one [Fig. 2], lung abscess [Fig. 3], inflamed lymph nodes = one), and one as false negative. This patient had an infected knee prosthesis (described previously as false-negative prostheses) with abscess formation between the femoral muscles. This muscle abscess was completely missed by immunoscintigraphy but was correctly detected by In-111 oxine-labeled leukocytes. Four patients with possible appendicitis were examined. The Tc-99m Fab' fragment identified three as true positive (Fig. 4) and one as false negative. Because of better anatomic resolution, increased uptake in the appendix was detected by SPECT 2 to 3 hours after infection, whereas correct detection was not possible with planar imaging. Because of the increased pressure, one peritiphilitic abscess secondary to appendical perforation was missed by immunoscintigraphy.

Vascular graft infections were easily identified in two patients (one aortic graft, one femoropopliteal graft). Immunoscintigraphy correctly identified the extent of the graft infection and the local start of the infection. In one patient, the Tc-99m Fab' fragment unexpectedly revealed increased activity projecting to the heart, indicating pericardial tracer accumulation.

Table 5 gives an overall statistical analysis of Tc-99m LeukoScan.

Regarding the diagnostic accuracy of Tc-99m Fab'

TABLE 2. Statistical evaluation of immunoscintigraphic findings in patients with suspected endocarditis

	LeukoScan (%)
Sensitivity	66
Specificity	79
Positive PV	26
Negative PV	87
Accuracy	78

Transthoracic/transesophageal echocardiography was used as gold standard for final diagnosis. TTE/TEE, transthoracic/transesophageal echocardiography; PV, predictive value.

TABLE 3. Immunoscintigraphy in Patients with Bone and Joint Infections

Patient	Age (years)	Sex	Fever (weeks)	ESR (mm/h)	Leukocyte count/mm ³	Localization	LeukoScan
1	47	M	3	72	10,200	Hip prosth.	-
2	49	M	4	33	8,800	Knee prosth.	+
3	71	F	8	39	11,800	Knee prosth.	+
4	52	M	2	51	11,150	Knee prosth.	+
5	74	M	11	49	11,200	Hip prosth.	-
6	69	F	9	51	9,200	Knee prosth.	+
7	55	F	5	41	—	Hip, soft tissue	+
8	61	M	7	49	9,300	Knee prosth.	-
9	34	F	10	44	9,200	Knee arthritis	+
10	29	F	13	35	10,000	Ankle synovitis	+
11	55	M	5	67	—	Knee synovitis	+
12	47	F	15	—	—	Knee synovitis	+
13	44	M	11	—	8,100	Ankle synovitis	+
14	31	F	6	44	8,500	Knee arthritis	+
15	49	F	5	—	—	Ankle synovitis	+
16	56	F	5	51	9,100	Distal tibia	+
17	61	F	7	45	10,100	Diaphyseal Femur	-
18	82	M	—	—	—	Diaphyseal Femur	-
19	45	F	14	33	9,900	Diaphyseal Humerus	+
20	61	M	9	—	13,000	Distal radius	+
21	44	M	6	34	—	Proximal tibia	+
22	38	F	7	45	12,100	Tibia	+
23	53	M	4	29	13,000	Diaphyseal humerus	-
24	41	F	7	51	9,600	Tibia	+
Mean	52.34		7.52	45.42	10,236.11		
x ± SD	13.65		3.50	11.06	1,485.40		

Normal values: WBC, 4.0–11.0 × 10⁹/l; ESR, <15 mm/h.

ESR, erythrocyte sedimentation rate; WBC, white blood cell count (leukocytes); Prosth., prosthesis; Soft-Tis., soft tissue; Dist, distal; Prox., proximal.

fragments and in vitro laboratory tests, no significant differences were found for the leukocyte count and the Westergren erythrocyte sedimentation rate in patients with endocarditis, infections of arthroplastic joints, natural joints, peripheral or central bones, and soft tissues (*P* = 0.37 to 0.44).

Mean uptake measurements were performed to quantify the percentage of the injected activity of the antibody 1, 4, and 24 hours after injection in the liver, spleen, kidney, bone marrow, and infective lesions. The

percentages of the injected activity in the liver were 11.6%, 8.8%, and 6.5%, respectively. The percentages in the spleen were 1.8%, 1.5%, and 1.1% respectively. They were 3.2%, 3.9%, and 2.0% in one kidney, and 2.0%, 1.8%, and 1.2% in a clearly defined bone marrow area. In the infective lesion, we found uptake decreasing over time (0.13%, 0.12%, and 0.08%). The target:background measurements showed increasing ratios over time of 1.7:1, 1.8:1, 2:1 for bone infection, and 2.6:1, 2.7:1, and 2.9:1 for soft tissue infection, respectively.

Nonspecific bowel uptake was described as false positive, with a visual intensity of uptake comparable to or less than that of the liver and spleen. In two cases, very faint uptake was seen 40 to 50 minutes after injection in the colon, whereas in most patients nonspecific bowel uptake was noted in the descending colon on average 3 hours after injection. All patients had nonspecific small or large intestinal uptake 24 hours after injection.

Discussion

Previous prospective investigations of our group have shown that Tc-99m antigranulocyte Fab' fragments can

TABLE 4. Statistical Evaluation in Bone and Joint Infections

LeukoScan	Prosthesis (%)	Peripheral Bones	
		(%)	Joints (%)
Sensitivity	63	66	100
Specificity	92	83	(100)
Positive PV	83	75	—
Negative PV	79	77	—
Accuracy	80	76	—

PV, predictive value.

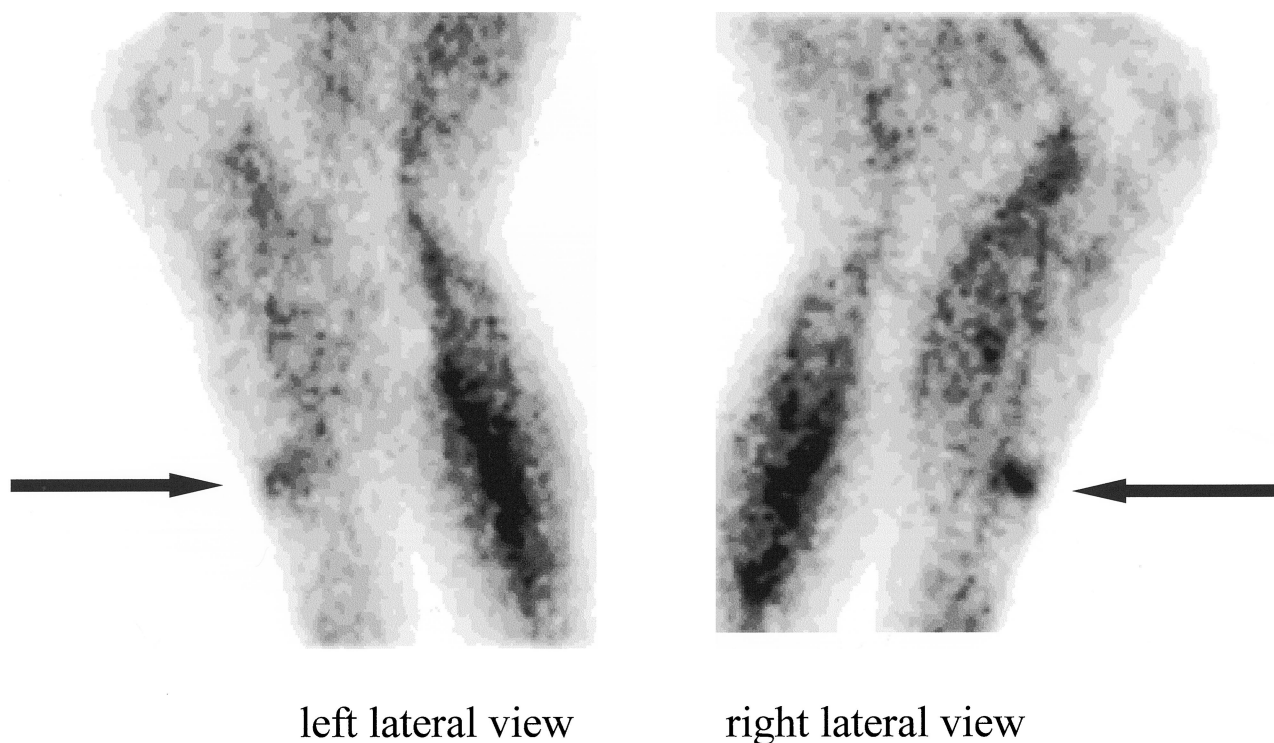


Fig. 2. Soft tissue fistula of the tibia without osteomyelitis.

be administered safely to patients. No adverse effects or human antimouse antibody formation were reported (17,18,27,28). In preselected groups of patients with possible infectious soft tissue or bone lesions, imaging with Tc-99m Fab' fragments revealed results superior to In-111 oxine-labeled and Tc-99m HMPAO-labeled leukocytes (17,18). In the past, similar results were obtained with Tc-99m-labeled complete monoclonal antibodies, with most experience gained using intact immunoglobulin G (BW 250/183; CIS, France) (5). The diagnostic accuracy of Tc-99m-labeled whole antibodies in soft tissue infections has been reported to be as great as 100% (6). Comparative studies in preselected patient groups proved Tc-99m Fab' fragments to be as reliable as intact immunoglobulin G (BW 250/183) (29).

Because more extensive studies are needed to further assess the clinical value of this new imaging method, we retrospectively evaluated the Tc-99m Fab' fragment results in a mixed patient population, with possible infection, as would normally be done in clinical practice. Diagnostic accuracy was compared with published data on intact antibodies and labeled leukocytes in preselected patient populations from the recent literature.

Prosthetic valve endocarditis constitutes 12% to 33% of reported cases of infective endocarditis (30–33). In the current study, the proportion of patients with valve replacement in the endocarditis group was much greater

(83%). Immunoscintigraphy with Tc-99m intact antibodies (BW 250/183) (34) has previously shown their potential for being an important and reliable diagnostic tool, with sensitivity, specificity, positive and negative predictive values of 79%, 82%, 79%, and 82%, respectively. In the current study, similar results were found (66%, 79%, 26%, and 87%, respectively) for Tc-99m Fab' fragments. The lower positive predictive value resulted from the timing of the scans, because SPECT images obtained 17 to 19 hours after injection showed increased residual blood-pool activity of circulating antibody fragments in the major vessels of the heart and aortic outflow. No differentiation between pathologic tracer accumulation in the inflammatory lesions and normal visualization of the hematopoietic bone marrow (thoracic spine, sternum, ribs) was possible, thus resulting in a higher number of false-positive results. Contrary to imaging infection of bone or soft tissue lesions, delayed (26 hours after injection) SPECT images of the thorax were needed for sufficient background clearance, which allowed the detection of small lesions with better imaging quality. As in the current study, immunoscintigraphy with intact antibodies has been shown (34) to be a valuable tool for indicating the degree of activity of the inflammatory processes, whereas echocardiography cannot reliably differentiate between active and quiescent vegetations (35–38). Thus, immunoscintigraphy with

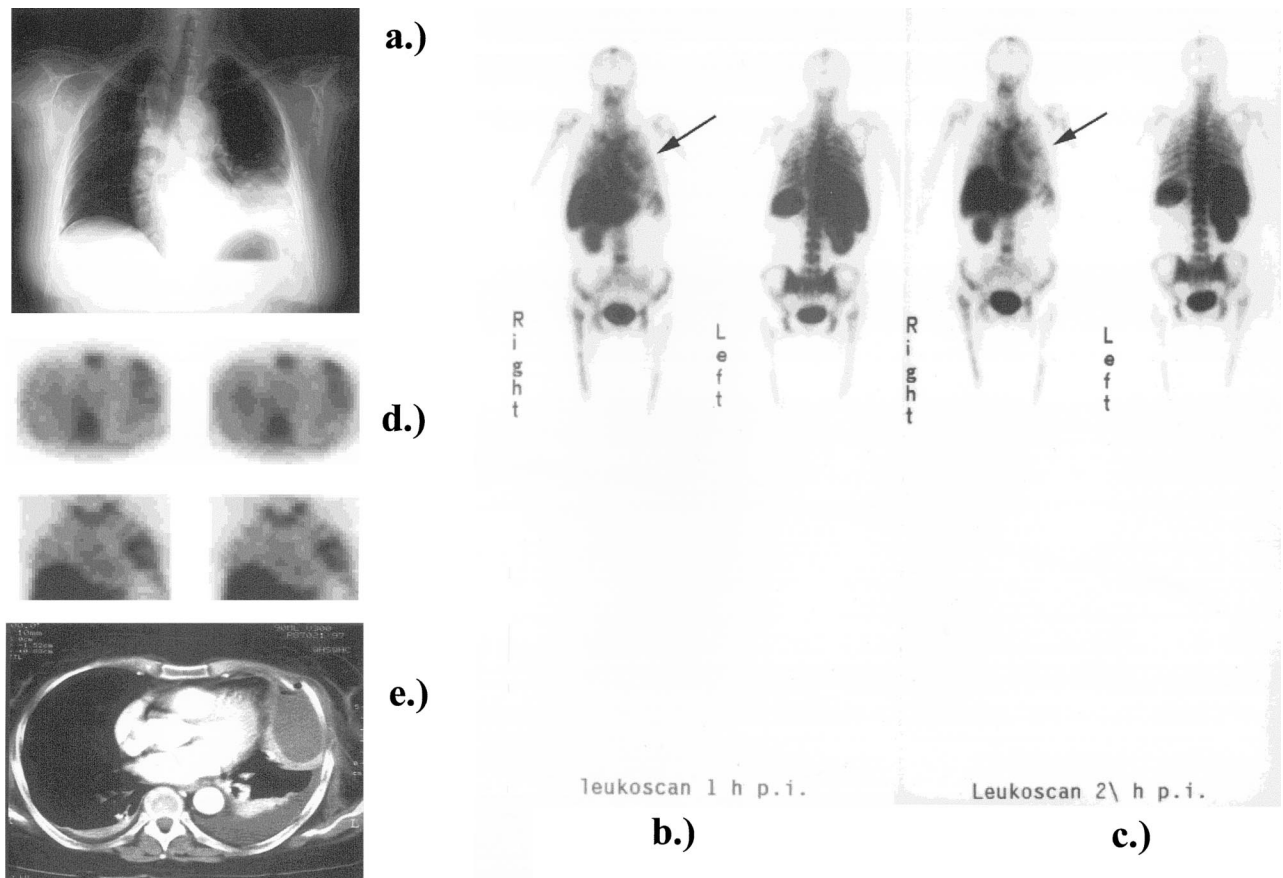


Fig. 3. A 59-year-old woman had an infected and loosened hip prosthesis. (A) Repeated planar radiographs of the thorax showed a wide radiopacity in the lower area of the left thorax, which was interpreted as pleural effusion. There was no sign of pneumonia. LeukoScan correctly excluded an infection of the hip. (B) Surprisingly, a whole-body scan showed intense uptake projecting to the lower left thorax 1 hour after injection, with an increase of intensity 2 hours after injection (C) at this area. (D) SPECT images obtained 18 hours after injection located this focus to the lower part of the left lung, close to the ribs. The nuclear medicine diagnosis was an abscess forming pneumonia. (E) This was confirmed by computed tomography.

Tc-99m-labeled antibody fragments should be used to complement echocardiography, because valuable additional information may be provided beyond echocardiography, especially when equivocal vegetations are demonstrated.

The sensitivity of immunoscintigraphy with Tc-99m monoclonal Fab' fragments in patients with bone and periprosthetic infections was 66% and 63%, respectively. Compared with data obtained from preselected patient populations, this is lower than Ga-67 (40) and Tc-99m nanocolloids (41) at 93%, than In-111 oxine labeled granulocytes (2) at 85%, and than In-111 human immunoglobulin at 86% in diabetic foot infections (15).

In the diagnosis of osteomyelitis, the specificity of Ga-67 (40) has been reported to be 83%, whereas that of Tc-99m-nanocolloid is 88% (41), In-111 oxine-labeled granulocytes is 85% (2), and In-111 human immunoglobulin (15) is 84%. In our study, Tc-99m monoclonal

Fab' fragments had a specificity of 92% in the diagnosis of osteomyelitis and periprosthetic infections.

The lower sensitivity of Tc-99m monoclonal Fab' fragments for infection in this study occurred because three patients had false-negative results in each bone-periprosthetic group. This occurred predominately in patients with post-traumatic diaphyseal long-bone infections and localized osteomyelitis in the bone shaft. A possible reason for the lack of uptake could be reduced vascularization as a result of lower capillary permeability at the site of infection and a higher prevalence of chronic infections in these patients, thus resulting in an environment less chemotactic for circulating granulocytes. Conversely, independent of the grade of infection, all patients with infections of the axial bones had photopenic areas at the respective sites of interest. The same results have been reported for intact antibodies in infants and adults (20,41) and for labeled leukocytes (41). Ga-67-

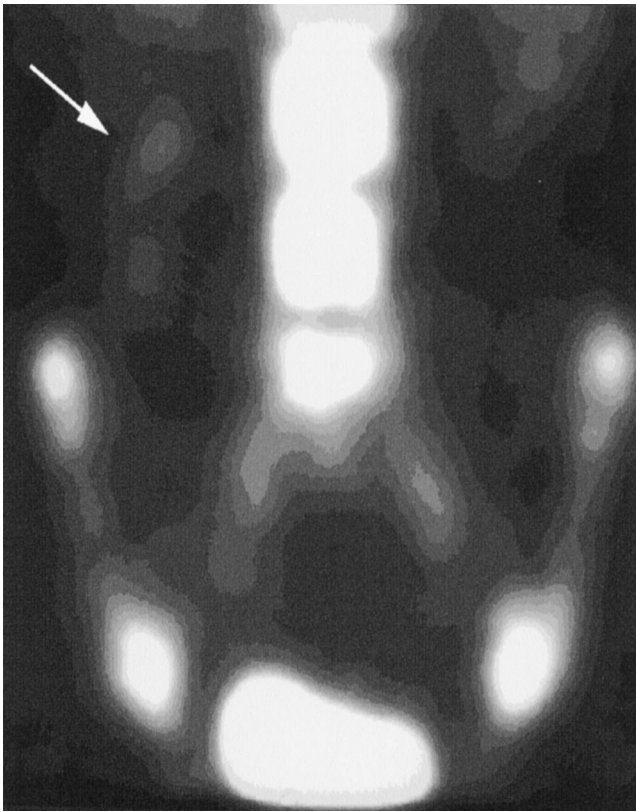


Fig. 4. A 24-year-old man had dislocated atypical appendicitis.

citrate scanning (41–45) is the only nuclear medicine imaging method with increased uptake in patients with spinal infections. An increase in sensitivity up to 88% with a commensurate decrease in specificity to 67% can be achieved when cold lesions in the spine are included as pathognomic for localization of disease. Instead, an equal increase in sensitivity without a decrease in specificity (86% and 85%, respectively) can be achieved when patients with arthritic and synovial infections are added, because all images with Tc-99m Fab' fragments were correctly positive for joint infections.

Physiologic bowel uptake harbors a certain potential

TABLE 5. Overall Statistic

LeukoScan	Overall Statistic (%)
Sensitivity	76
Specificity	84
Positive PV	61
Negative PV	81
Accuracy	78

PV, predictive value.

for misinterpretation of Tc-99m monoclonal Fab' fragment scanning. In a few patients, very faint and diffuse uptake in the colon can be expected as early as 40 to 60 minutes after injection. In most patients, however, the nonspecific uptake is localized in the descending colon at a mean of 3 hours after injection. Using SPECT easily solves this potential problem. A correct differentiation between nonspecific bowel uptake and atypical appendicitis is easily possible, because of better anatomic resolution.

Good results with Tc-99m Fab' fragments were achieved in patients with soft tissue and vascular graft infections. This is important, because the accuracy of diagnosis of atypical appendicitis has improved little in decades, with 10% to 20% of operated patients having either a perforated or uninflamed appendix (46). In patients with atypical appendicitis, Tc-99m HMPAO-labeled and In-111 oxine-labeled leukocytes (47,48) and monoclonal antibodies (49) have demonstrated sensitivities, specificities, and accuracies of 85% to 92%, 93%, 89%, respectively, and 71%, 73%, and 72%, respectively. In this particular group of patients, a statistical evaluation of Tc-99m Fab' fragment scanning is not possible because of the small number of patients. Imaging of atypical appendicitis with SPECT 2 to 3 hours after injection, however, made a correct diagnosis easy because of excellent imaging quality, with results comparable to those obtained with intact antibodies (49). Although two patients with peripheral vascular graft infections are obviously not sufficient for statistical evaluation, planar immunoscintigraphy with Tc-99m Fab' fragments resulted in images with very high anatomic resolution and morphologic clarity at only 1 to 4 hours after injection. Thus, important information on the extent of infection and the initial site of infection of the vascular graft could be obtained. This is a result of the rapid uptake into the lesion and fast renal excretion of background activity, as is supported by our target:background data. So far, similar or even lower results for sensitivity and specificity (and accuracy), were reported for Tc-99m HMPAO-labeled (50) and In-111 oxine-labeled (51) leukocytes, at 53% and 100% (66%), and 67% and 97%, respectively.

Summarizing our findings, the sensitivity and specificity of Tc-99m Fab' fragment scanning in soft-tissue and vascular infections were superior to those reported in the literature for labeled leukocytes. A possible reason for this could be better vascularization of these lesions and a greater prevalence of acute infections in these patients (29). The findings of the current study in this particular group of patients are similar to those from studies using Tc-99m-labeled intact immunoglobulin G antibody (BW 250/183), where the diagnostic accuracy reached 100% for soft tissue infections (52). Thus, the

Tc-99m Fab' fragment proved to be as reliable as labeled leukocytes and intact immunoglobulin G (BW 250/183), as reported in the literature (29).

Results from Tc-99m Fab' fragment scanning in patients with osteomyelitis and periprosthetic bone infections were slightly less encouraging. Bone infections are often diagnosed at advanced stages, with the beginning of chronic infection. Leukocyte imaging and immunoscintigraphy using Tc-99m-labeled intact immunoglobulin G (BW 250/183) antibodies have sensitivity rates of only approximately 50% (6,7,8,11,29). Compared with these studies, results obtained with Tc-99m-labeled Fab' fragments were superior.

Conclusion

The overall sensitivity, specificity, and diagnostic accuracy of LeukoScan was comparable to published data of In-111 oxine-labeled and Tc-99m HMPAO-labeled leukocytes and to intact immunoglobulin G (BW 250/183). Findings obtained using LeukoScan appear to be superior to those obtained with available techniques for the detection of soft tissue infections, with comparable results in the other groups. No human antimouse antibody formation was observed after repeated use, and furthermore the method does not require ex vivo blood handling, thus making it a safe, simple, and easy-to-handle test.

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