Clinical Value of Immunoscintigraphy in Patients with Fever of Unknown Origin

Johannes Meller, Velemir Ivancevic, Monika Conrad, Stefan Gratz, Dieter Ludwig Munz and Wolfgang Becker
Department of Nuclear Medicine, Georg August University of Göttingen, Göttingen; and Clinic and Policlinic of Nuclear Medicine, Charité, Humboldt University, Berlin, Germany

The aim of our study was to evaluate the clinical value of immunoscintigraphy with the monoclonal antibody ^{99m}Tc-BW 250/183 in patients with fever of unknown origin (FUO). The antibody BW 250/183 is an immunoglobulin G_1 subtype that binds to the antigen NCA-95, which is expressed on the cell membrane surface of granulocytes. **Methods:** We studied 51 patients who were referred with the diagnosis of FUO. Thirty-five percent of the patients suffered from infection, 17% had autoimmune diseases, 14% had neoplasms and 8% had other diseases. The remaining 28% of the patients did not have a diagnosis. Planar imaging was performed in all patients, and 19 patients underwent SPECT. In our analysis, both cold and hot spots were considered diagnostic. **Results:** Pyogenic infections were visualized correctly in 13 foci. The diagnosis of endocarditis (n = 4) could be determined only by SPECT. False-negative results were found in 4 patients and false-positive uptake was seen in 2 patients. No false-positive uptake or cold spots in the central bone marrow were found in patients with viral, granulomatous and autoimmune diseases or in those patients in whom no FUO cause was found in a 6-mo follow-up. In these patients, a negative scan did not change their diagnostic work-up. Cold spots in the central bone marrow were correctly interpreted in 5 of 6 patients. Sensitivity in detecting pyogenic foci was 73% and specificity was 97%. Positive and negative predictive values were 93% and 87%, respectively. Including areas of decreased uptake in the analysis, sensitivity for detecting an underlying inflammatory or malignant process for FUO was 81% and specificity was 87%. Positive and negative predictive values were 81% and 87%, respectively. **Conclusion:** Immunoscintigraphy with ^{99m}Tc-BW 250/183 in patients with FUO has clinical potential for the diagnosis and exclusion of pyogenic causes of FUO. Metastatic malignant disease and high-grade spondylodiskitis could be diagnosed early in a diagnostic work-up by a characteristic cold spot pattern in the bone marrow. SPECT is indispensible for scintigraphic imaging of endocarditis.

Key Words: fever of unknown origin; immunoscintigraphy; technetium-99m-antigranulocyte-antibody; monoclonal antibody; SPECT; iterative reconstruction

J Nucl Med 1998; 39:1248–1253

Fever of unknown origin (FUO) is defined as recurrent fever of 38.3°C or greater, lasting 2–3 wk or longer and undiagnosed after 1 wk of hospital evaluation (*1*). Prolonged undiagnosed fever is usually an atypical manifestation of more common diseases rather than a manifestation of an exotic illness.

The three most common causes of fever are infection, neoplasm and autoimmune or collagen vascular diseases (*1,2*). Malignant diseases have now replaced infection as a leading cause of FUO. Nevertheless, in some larger studies, the prevalence of infection in patients with FUO is up to 50% (*2*). Previous studies used ^{67}Ga (*3–6*), ^{111}In white blood cell (WBC) scans (*7–11*) and ^{111}In-labeled human immunoglobulin (HIG) scintigraphy (*12*) in FUO patients.

The murine monoclonal antibody BW 250/183 has been successfully used to diagnose musculoskeletal infection (*13,14*), inflammatory bowel disease (*15,16*) and infective endocarditis (*17*). Recently, Becker et al. (*18*) published the first results of using the monoclonal antibody ^{99m}Tc-BW 250/183 in patients with FUO using planar scintigraphy. In Becker's patients, the diagnostic value of photopenic lesions was not examined.

The aim of our study, using the same monoclonal antibody, was to gather more information about the clinical value of this method for FUO patients, including the use of SPECT and using a different approach to interpret photopenic bone marrow lesions in a series of patients with FUO who had an intermediate prevalence (35%) of pyogenic infections.

MATERIALS AND METHODS

This study is a retrospective analysis of 51 patients (age range 2–75 yr; median age 41 yr) who underwent immunoscintigraphy of inflammation between January 1989 and July 1995.

The patients were referred with the diagnosis of FUO by the department of internal medicine (n = 39), the pediatric department (n = 6) and other departments (n = 2) of our university. Four patients were referred from other hospitals. Criteria for inclusion in this study were: monosymptomatic fever of a 38.3°C or greater lasting more than 2 wk and no established diagnosis after at least 1 wk in the hospital.

The duration of fever was 22 days–15 yr (median duration 8 wk). Twelve of the 51 patients received antibiotic or immunosuppressive therapy for more than 1 wk before immunoscintigraphy.

The diagnostic evaluation of the patients before scintigraphy included at least routine blood chemistry, radiographic studies, serological and bacteriologic tests and abdominal ultrasound examination. Final diagnosis was established by clinical follow-up, radiography, CT, MRI, echocardiography, endoscopy, biopsy, surgery, culture or serological tests. Full hospital records and a follow-up of at least 6 mo were available for all patients. Thirty-five percent (18 of 51) of the patients had infection, 16% (8 of 51) autoimmune diseases, 14% (7 of 51) neoplasms and 8% (4 of 51) other diseases. Fever remained unexplained in 27% (14 of 51) of the patients.

The murine monoclonal antibody BW 250/183 (Behringwerke, Marburg, Germany) was used for immunoscintigraphy. BW 250/183 is an immunoglobulin G_1 subtype that binds to the antigen NCA-95, a surface glycoprotein with a molecular weight of 95 kD that appears early in the differentiation of granulopoietic cells and is expressed on the cell membrane surface of almost all human granulocytes and their more mature precursors.

According to the manufacturer's recommendation, 250–500 μg of the intact antibody were labeled with 550 MBq ^{99m}Tc-pertechnetate and injected intravenously. In all patients, scintigraphy was

Received Mar. 12, 1997; revision accepted Oct. 13, 1997.
For correspondence or reprints contact: Wolfgang Becker, MD, Department of Nuclear Medicine, University of Göttingen, Robert Koch-Str. 40, D-37075 Göttingen, Germany.

TABLE 1
Patients with Increased Tracer Uptake

Patient no.	Age (yr)	Sex	Scintigraphic findings (increased uptake)	Scintigraphic diagnosis	Final diagnoses	Diagnosis verified by
1	22	F	Left sacroiliac joint	Pyogenic sacroileitis	Pyogenic sacroileitis	MRI, C
2	8	F	Right maxillary sinus	Sinusitis	Sinusitis	S, C
3	75	F	Tip of pacemaker lead	Infective endocarditis	Infective endocarditis	TEE, C, S
4	48	M	Heart valves	Infective endocarditis	Infective endocarditis	TEE, C, S
5	50	F	Heart valves	Infective endocarditis	Infective endocarditis	TEE, C
6	2	M	Terminal ileum	Ileitis	Salmonellosis	C, SE
7	10	F	Right ascending colon	Colitis	Salmonellosis	C, SE
8	4	M	Pelvis	Abscess	Abscess, salmonellosis	C, S, CT
9	63	F	Liver, Sheldon catheter	Hepatic abscess, catheter infection	Hepatic abscess, sepsis, catheter infection, (*Candida albicans*)	C, US, SE
10	60	F	Colon	Colitis	Ulcerative colitis	EN
11	58	M	Upper abdomen	Abscess	Paracolonic abscess due to colorectal cancer	S, C
12	67	F	Pelvis	Abscess	Carcinoma of the sigmoid	S
13	27	M	Mediastinum	Mediastinitis	Teratoma	S
14	74	M	Heart valves	Infective endocarditis	Infective endocarditis	TEE, C

C = culture; S = surgery; TEE = transesophageal echocardiography; SE = serology; US = ultrasound; EN = endoscopy.

performed between (mean ± s.d.) 4 ± 1 hr and 22 ± 2 hr after injection.

Planar scans of the head, chest, abdomen and extremities were performed in the anterior and posterior projections using a single-head (SX 100; Picker International, Ohio) or a double-head (PRISM 2000; Picker) gamma camera fitted with a parallel-hole, high-resolution and low-energy (LEHR) collimator (128 × 128 matrix, 300–500 kcts/image; whole-body scans were performed with an acquisition time of 30 min). In 19 patients, SPECT images of the thorax (n = 17) or abdomen/pelvis (n = 2) were obtained 24 hr postinjection using a single-head (ECAT; Picker) or a double-head (PRISM 2000) gamma camera fitted with LEHR collimators (360° circular orbit, 60 stops at 30 sec per stop, 64 × 64 or 128 × 128 matrix). SPECT reconstruction using an Odyssey 2000 (Picker) computer system was done both by filtered backprojection (low pass/ramp) and by iterative reconstruction (ISA) described elsewhere (*19*) using eight iterative steps and attenuation correction.

In the first step of analysis, a scan was considered true-positive when abnormal accumulation of the tracer outside organs of physiologic uptake (liver, spleen, bone marrow, kidneys and bladder) was confirmed by further investigation as representing a pyogenic cause of fever. A scan was considered false-positive when abnormal uptake represented a noninfectious process. A true-negative scan was a normal immunoscintigraphic study, in which noninfective causes of FUO were established by further investigations. A false-negative scan was a normal study, in which a pyogenic cause for FUO was demonstrated subsequently.

In the second step of analysis, photopenic lesions in the central bone marrow were included in the analysis using the following interpretation: Multiple cold spots in the bone marrow were considered to represent malignant disease (*20–22*). Decreased uptake in two adjacent segments of the spine was considered to be spondylodiskitis. This interpretation was adopted because of the way infection normally spreads from the intervertebral disk to adjacent vertebral bodies due to the special blood supply of the vertebral column (*23*). A single cold spot in the bone marrow was considered to represent an infective rather than a malignant cause (*14*). A scan was regarded as true-positive if abnormal accumulation of the tracer outside organs of physiologic uptake represented a pyogenic cause for fever or decreased uptake in the bone marrow was correctly interpreted to represent either an inflammatory or malignant process with reference to the criteria cited earlier. A scan was regarded as false-positive when abnormal uptake represented a noninfectious process or if no correct interpretation of decreased uptake in the bone marrow could be given. A true-negative scan was a normal immunoscintigraphic study in which noninfectious causes of FUO were established by further investigations. A false-negative scan was a normal study in which further evaluation revealed pyogenic inflammation or metastatic disease in the bone marrow as a cause of FUO.

RESULTS

The patient data including scintigraphic findings and their interpretation compared with final diagnoses are shown in Tables 1–3. A 35% prevalence of pyogenic inflammation was found in our series.

Pyogenic infections as a cause of FUO were correctly visualized in 12 patients (13 foci). Infective endocarditis was successfully imaged in 4 of 5 patients. Vegetations were >8 mm in diameter, and the diagnosis was proven by transesophageal echocardiography (TEE) culture, clinical course and surgery in 2 patients. The diagnosis of endocarditis could be made only using SPECT. Filtered backprojection and ISA revealed full concordance with the results. Three of 5 abdominal abscesses could be correctly diagnosed by immunoscintigraphy. In 1 patient (Patient 9, Table 1), hepatic abscess was observed by scintigraphy 5 days before ultrasound showed an anechoic lesion at the inflammation site. In other patients who were true-positive by scintigraphy, their ultrasounds and CT scans were false-negative or misleading. For example, paracolic abscess (Patient 3, Table 1) infiltrating the spleen was regarded as a splenic infarction by CT. In 3 patients, inflammatory bowel disease as a cause of FUO was correctly imaged by immu-

TABLE 2
Patients with Decreased Tracer Uptake in Central Bone Marrow

Patient no.	Age (yr)	Sex	Scintigraphic findings (decreased uptake)	Scintigraphic diagnosis	Final diagnoses	Diagnosis verified by
15	40	F	Right sacroiliac joint	Pyogenic sacroileitis	Pyogenic sacroileitis	BS, C
16	74	M	Thoracic vertebrae (T8-9)	Spondylodiskitis	High-grade spondylodiskitis	S, H, C
17	64	F	Multiple foci of decreased uptake	Neoplasm	Non-Hodgkin's lymphoma	H
18	67	F	Multiple foci of decreased uptake	Neoplasm	Bone marrow metastases, small-cell lung cancer	MRI
19	50	M	Multiple foci of decreased uptake	Neoplasm	Bone marrow metastases (carcinoma of the sigmoid)	H, MRI
20	24	M	Thoracic vertebra (T9)	Spondylitis	Fatty infiltration of the bone marrow	MRI

BS = bone scintigraphy; H = histology; C = culture; S = surgery.

noscintigraphy 22 ± 2 hr after injection of the radiopharmaceutical. In one patient, ulcerative colitis already was diagnosed, but neither a barium enema nor endoscopy, including biopsy, could show current inflammatory processes. In contradistinction to these findings, immunoscintigraphy detected granulocytic infiltration of the whole colon. The clinical course after immunosuppressive medication revealed that in this patient highly acute ulcerative colitis was the only cause of monosymptomatic fever.

False-negative results were obtained in 4 patients (endocarditis, hepatic abscess, pancreatic abscess and pyogenic interstitial nephritis). In 2 patients, a false-positive accumulation of the tracer was seen in malignant disease (mediastinal teratoma and sigmoid carcinoma). No false-positive uptake occurred in viral, granulomatous and autoimmune diseases. Furthermore, no false-positive uptake or cold spots in the central bone marrow occurred in those patients in whom no cause of FUO could be found at a 6-mo follow-up. In these patients, the fever resolved without any specific therapy. Negative scans did not change the diagnostic work-up in these patients because the referring physicians were aware that a scan could be helpful, but it would not definitively exclude pyogenic inflammation.

Decreased activity in the central bone marrow was verified in 6 patients. The underlying process was correctly interpreted in 5 patients (malignant disease in 3 patients, inflammation in 2 patients). In 1 patient, a focal cold spot in the thoracic spine, which represented a fatty infiltration of the bone marrow, was misinterpreted as osteomyelitis.

Results of SPECT reconstruction done either by filtered backprojection or ISA algorithm were fully concordant in all patients. Five true-positive, 2 false-negative and 12 true-negative scans were obtained. These results included endocarditis (true-positive: 4 patients, false-negative: 1 patient) and abdominal abscesses (true-positive: 1 patient, false-negative: 1 patient).

With reference to the analysis proposed previously, sensitivity for detecting pyogenic foci was 73% and specificity was 97%. Positive and negative predictive values were 93% and 87%, respectively.

When areas of decreased uptake were included in the analysis, sensitivity for detecting underlying inflammatory or malignant processes, as causes of FUO, was 81% and specificity was 87%. Positive and negative predictive values were 81% and 87%, respectively.

TABLE 3
Patients with Normal Scans

Disease (no. of patients)	Age (yr)	Sex (no. of patients)	Final diagnoses	Diagnosis verified by (no. of patients)
Pyogenic disease (4)	10–59	M (1) F (3)	Infective endocarditis (n = 1), hepatic abscess (n = 1), pancreatic abscess (n = 1), pyogenic interstitial nephritis (n = 1)	TEE (1), C (3), S (1), SE (1), CT (1), H (1)
Various diseases (8)	40–57	M (6) F (2)	Tuberculosis (n = 1), prolonged virus infection (n = 1), cytomegalic infection (n = 1), brucellosis (n = 1), foreign body reaction (n = 1), granulomatous hepatitis (n = 1), self-induced fever (n = 1), renal cell carcinoma (n = 1)	CL (3), S (2), SE (2), H (1)
Autoimmune disease (8)	2–67	M (2) F (6)	Autoimmune hemolytic anemia (n = 1), chronic relapsing neuropathy (n = 1), Still's disease (n = 4), Horton's disease (n = 1), rheumatoid arthritis (n = 1)	CL (6), X-ray (1), S (8)
FUO (14)	2–72	M (7) F (7)	No cause found for FUO	US (14), CT (13), SE (14), TEE (3), EN (8), H (3), C (13), MRI (2)

C = culture; S = surgery; EN = endoscopy; SE = serology; BS = bone scintigraphy; US = ultrasound; TEE = transoesophageal echocardiography; H = histology; CL = clinical course.

DISCUSSION

The ideal radiolabeled agent for imaging inflammation in patients with FUO should, despite a high photon flux, have a radiation burden as low as possible and the diagnosis should be available as soon as possible. In the FUO context, that shows a wide range of underlying diseases. It would not be disadvantageous if the radiotracer was trapped in other than inflammatory (e.g., malignant) foci. Even the absence of accumulation of the radiopharmaceutical at sites that normally show a physiologic uptake of the tracer can give further information about the underlying pathology.

For example, ^{67}Ga images acute, chronic and granulomatous inflammation, but it also accumulates in various malignant diseases (*24*) that are known to be potential FUO causes. On the other hand, ^{67}Ga yields a considerable radioactive burden for the patient and is excreted into the bowel with possible superimposition and pathologic foci in planar scans.

Scans with ^{111}In WBC are highly sensitive and specific for diagnosing acute and chronic inflammations (*25,26*). Occasional accumulation of the tracer can be found in malignant disease, contributing to the final diagnosis in patients with FUO (*11*). Although cold spots in the central bone marrow are considered an unspecific finding in ^{111}In WBC scintigraphy (*27*), they should not be rejected as nondiagnostic if their value in detecting metastatic or chronic inflammatory disease is considered. Unfortunately, labeling blood cells with ^{111}In-oxine is time-consuming and the photon flux of ^{111}In WBC is too low to enable SPECT acquisition.

Scans with ^{111}In-labeled HIG (*12*), which has not been commercially available until recently, could be useful in particular patient subgroups (e.g., granulocytopenic patients or HIV-positive patients).

Compared to other compounds, ^{99m}Tc-BW 250/183 has the advantage of rapid availability. SPECT acquisition is possible, even 24 hr postinjection due to the high photon flux of ^{99m}Tc. Furthermore, the low background activity enables imaging of inflammatory foci with a high target-to-background ratio. Due to superior targeting of the central bone marrow, where approximately 55% of the radiolabeled antibodies are bound, cold spots can be detected with higher accuracy than with other techniques (*21*).

In our series, 13 foci in 12 patients were correctly imaged by immunoscintigraphy. In all of these patients, granulocytic infiltration either had been assumed or was proven by further evaluation (Figs. 1 and 2). Infective endocarditis could be diagnosed using only SPECT, which is concordant with the findings of Morguet et al. (*17*). Infective endocarditis accounted for the high rate of false-negative immunoscintigraphic scans in the series examined by Becker et al. (*18*) who used planar scintigraphy in their patients with FUO. An ISA that has proved superior to filtered backprojection in various circumstances (*28,29*) showed no advantage in showing infective endocarditis (Fig. 3). In our patients, 3 of 5 abdominal abscesses were correctly diagnosed by immunoscintigraphy. In these patients, ultrasound and CT were false-negative or misleading in the diagnosis. These observations support the results of previous studies that compared ^{111}In WBC scans with ultrasound and CT (*25,26*). In our series, inflammatory bowel disease as a cause of FUO was correctly imaged in 3 patients 22 ± 2 hr after injection of the radiopharmaceutical. Immunoscintigraphy proved useful especially in children with salmonellosis and ulcerative colitis with an atypical clinical course. These findings are concordant with previous data in which immunoscintigraphy was useful for diagnosing inflammatory bowel disease, although its accuracy was lower than with ^{111}In WBC scintigraphy and imaging with ^{99m}Tc-labeled leukocytes (*15,16*).

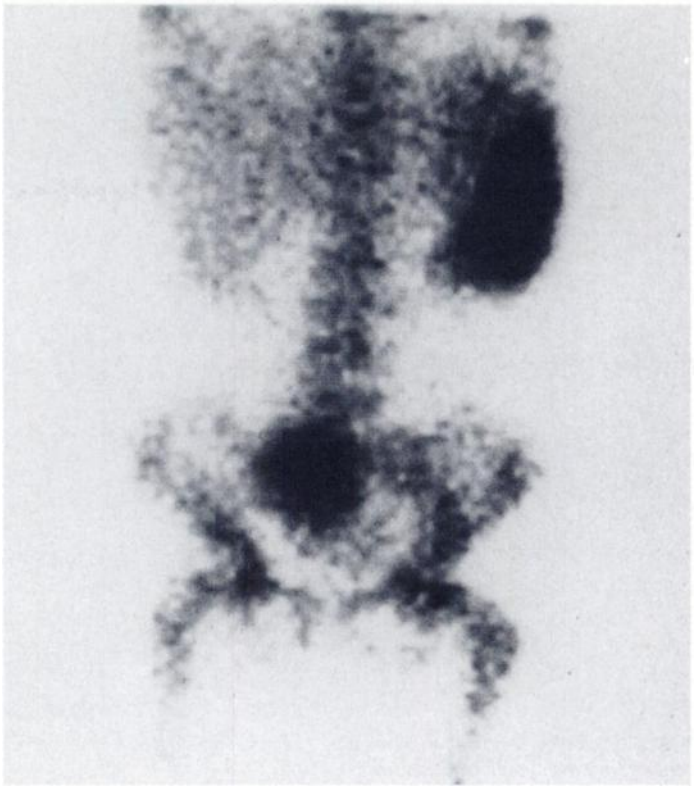

FIGURE 1. Planar scan of pelvic abscess caused by salmonellosis in 4-yr-old child, which was observed 4 hr after injection.

Cold spots in the central bone marrow found by ^{111}In WBC scintigraphy are associated with a wide range of pathological

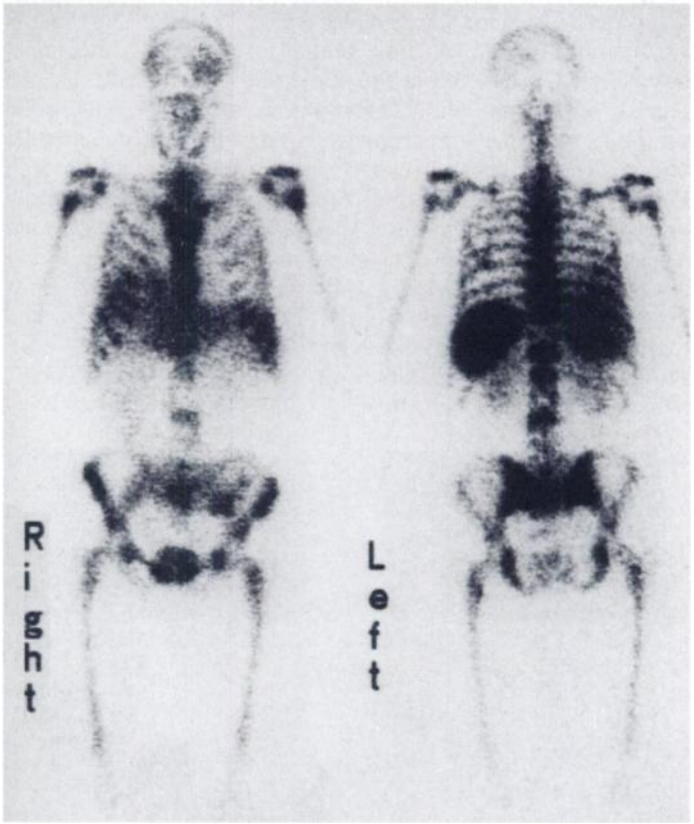

FIGURE 2. Whole-body scan shows multiple cold spots in thoracic and lumbar spine indicating bone marrow metastasis. False-positive accumulation of tracer was in sigmoid carcinoma.

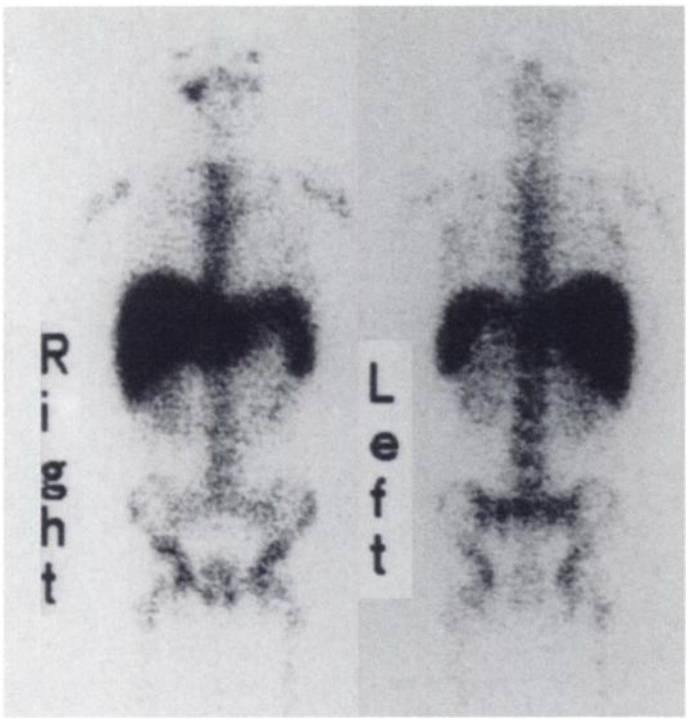

FIGURE 3. Whole-body scan obtained 22 hr after injection in 8-yr-old child shows sinusitis in right sinus maxillaris.

conditions including infection, metastatic disease, fracture, postradiation therapy changes, surgical interventions, Paget's disease and degenerative disk disease (*27,30,31*). This also proved true for immunoscintigraphy with MAb ^{99m}Tc-BW 250/183 (*13,21*). Decreased uptake is usually considered nondiagnostic. In these patients, dual-isotope imaging with ^{111}In WBC and ^{99m}Tc-sulfur colloid (*32*) could be helpful in the diagnosis. Combined scintigraphy with ^{99m}Tc-BW 250/183 and ^{99m}Tc-sulfur colloid has the potential for reducing nondiagnostic studies, but data about this topic are not available. On the other hand, the amount and configuration of cold spots in the central bone marrow represent important information about the underlying process, especially when screening patients with FUO. In our patients, widespread photopenic bone marrow lesions were correctly interpreted as representing malignant disease (Fig. 4). In these patients, immunoscintigraphy established the diagnosis of malignant disease early in their diagnostic work-up. As known from ^{111}In WBC scintigraphy and recently shown in immunoscintigraphy with ^{99m}Tc-BW 250/183 (*33*), spondylitis predominantly presents as a photopenic defect rather than as increased uptake in the central bone

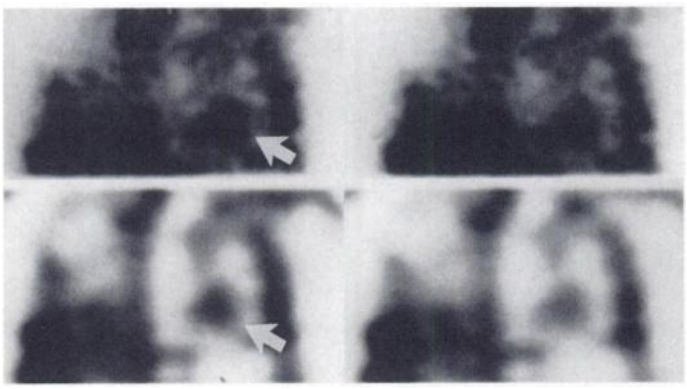

FIGURE 4. Colonal slices of image show infective endocarditis in projection to tip of pacemaker with lead shown with ISA (top) and filtered back reconstruction (bottom). SPET was performed 24 hr after injection.

marrow. This may be due to delayed scintigraphy when the initial granulocytic response has been replaced by a lymphocytic/monocytic response. Destruction of the central bone marrow by septic infarction, reduced influx of labeled granulocytes and circulating free antibodies, as a result of disturbed microcirculation, also has been proposed as the underlying process (*31*). Decreased uptake in two adjacent segments of the spine, as seen in one patient, although highly predictive of vertebral osteomyelitis (*33*), is an infrequent pattern of spondylitis on immunoscintigraphy. In our series, pyogenic sacroileitis showed the same scintigraphic pattern as vertebral osteomyelitis. The diagnosis was made in one patient (duration of fever: 3 wk) who had increased uptake in the left sacroiliac joint, whereas another patient (duration of fever: >4 wk) presented with decreased uptake in the right sacroiliac joint. Despite a lack of published immunoscintigraphic data, especially for sacroileitis, these observations are in concordance with the findings of Schauwecker (*34*), who demonstrated that sensitivity of ^{111}In WBC scintigraphy in chronic osteomyelitis was significantly lower in the central skeleton (containing active bone marrow) than in the peripheral bones because of increasing incidence of photopenic lesions. The same observations were made by Reuland et al. (*14*) using ^{99m}Tc-BW 250/183. The instance of a false-positive interpretation of a focal cold spot in a thoracic vertebra as osteomyelitis in a patient, which was proven to represent fatty infiltration of the bone marrow by MRI, underlines the difficulties that may appear if an unspecific finding like photopenia is included in the scintigraphic analysis.

Immunoscintigraphy failed to detect histologically proven pyogenic interstitial nephritis and one hepatic abscess. These false-negative findings are probably because of the high physiologic accumulation of radiotracer in the kidneys and liver. In addition, a chronic pancreatic abscess could not be detected by immunoscintigraphy even using SPECT (filtered backprojection and ISA). In this patient, labeled granulocytes or free-circulating antibodies were probably not able to pass through the thick wall of the chronic abscess formation. False-positive uptake was seen in a mediastinal teratoma infiltrated by a large amount of eosinophiles, possibly cross-reacting with the antibody, and in a carcinoma of the sigmoid (Fig. 2). This was probably caused by granulocytic infiltration of the tumor, an observation also known from ^{111}In WBC scintigraphy (*35*).

Studies in FUO patients performed with either ^{67}Ga (*3–6*) or ^{111}In-labeled WBC (*7–11*) revealed a wide range of sensitivities (34% to 75% and 17% to 85%, respectively). These discrepancies may be explained by the small and different patient populations, generally including no more than 35 patients who suffered from a wide spectrum of diseases. In the study recently published by Becker et al. (*18*), who performed immunoscintigraphy with ^{99m}Tc-BW 250/183 in 34 patients with FUO, the overall diagnostic sensitivity was low (40%) despite a 58.8% prevalence of inflammatory causes for FUO. This striking difference, compared to our results, may be partly explained by the fact that SPECT was not performed in these patients. Therefore, diagnoses in 6 patients suffering from endocarditis were missed. It is debatable if the vegetations were >5 mm in diameter, as was common in these patients, that they would have been detected by SPECT.

CONCLUSION

Immunoscintigraphy performed with the monoclonal antigranulocyte antibody ^{99m}Tc-BW 250/183 is a useful diagnostic tool in patients with FUO in the following conditions: in endocarditis, scintigraphy could contribute to the final diag-

noses if SPECT was performed in cases of doubtful findings in TEE. Immunoscintigraphy was superior to sonography and CT in the early detection of abdominal abscesses. Immunoscintigraphy was able to exclude pyogenic processes with high accuracy in those patients with autoimmune disease, which is of particular interest in syndromes like Still's disease, in which no established serologic marker of diagnosis existed until now. Metastatic malignant disease as a common cause of FUO may be diagnosed and differentiated from other underlying diseases by a characteristic pattern of multiple cold spots in the central bone marrow early in diagnostic work-up. A differentiated analysis of photopenic defects in the bone marrow should be included in the final scintigraphic interpretation.

REFERENCES

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine* 1961;40:1–30.
2. Smith JW. Southwestern internal medicine conference: fever of undetermined origin: not what it used to be. *Am J Med Sci* 1986;292:56–64.
3. Hilson AJW, Maisey MN. Gallium-67 scanning in pyrexia of unknown origin. *Br Med J* 1979;4:1330–1331.
4. Knockaert DC, Mortelmans LA, De Roo MC, Bobbaers AD. Clinical value of ^{67}Ga scintigraphy in investigation of fever or inflammation of unknown origin in ultrasound and computed area. *Acta Clin Belg* 1989;44:91–98.
5. McNeil BJ, Sanders R, Alderson PO, et al. A prospective study of CT, ultrasound, and gallium imaging in patients with fever. *Radiology* 1981;139:647–653.
6. Sfakianakis GN, Al-Sheikh W, Heal A, Rodman G, Zeppa R, Serafini A. Comparisons of scintigraphy with indium-111 leukocytes and ^{67}Ga in the diagnosis of occult sepsis. *J Nucl Med* 1982;23:618–626.
7. Davies SG, Garvie NW. The role of indium-labeled leukocyte imaging in pyrexia of unknown origin. *Br J Radiol* 1990;63:850–854.
8. Haentjens M, Piepsz A, Schell-Frederick E, Perlmutter-Cremer N, Frühling J. Limitations in the use of indium-111-oxine-labeled leukocytes for the diagnosis of occult infection in children. *Pediatr Radiol* 1987;17:139–142.
9. Hawker RJ, Hall CE, Drolc Z, Rhys-Evans PH. Indium leukocyte imaging in true pyrexia of unknown origin. *Eur J Nucl Med* 1985;10:172–174.
10. Schmidt KG, Rasmussen JW, Sørensen PG, Wedebye IM. Indium-111 granulocyte scintigraphy in the evaluation of patients with fever of undetermined origin. *Scand J Infect Dis* 1987;19:339–345.
11. Syrjälä MT, Valtonen V, Liewendahl K, Myllylä G. Diagnostic significance of indium-111 granulocyte scintigraphy in febrile patients. *J Nucl Med* 1987;28:155–160.
12. Oyen WJ, Claessens RA, Raemaekers JM, de Pauw BE, van der Meer JW, Corstens FH. Diagnosing infection in febrile granulocytopenic patients with indium-111 labeled human immunoglobulin. *J Clin Oncol* 1992;10:61–68.
13. Hotze A, Briele B, Overbeck B, et al. Technetium-99m-labeled antigranulocyte antibodies in suspected bone infections. *J Nucl Med* 1992;33:526–531.
14. Reuland P, Winker KH, Heuchert T, et al. Detection of infection in postoperative orthopedic patients with technetium-99m-labeled monoclonal antibodies against granulocytes. *J Nucl Med* 1991;32:2209–2214.
15. Almers S, Granerus G, Franzen L, Ström M. Technetium-99m scintigraphy: more accurate assessment of ulcerative colitis with exametazime-labelled leukocytes than with antigranulocyte antibodies. *Eur J Nucl Med* 1996;23:247–255.
16. Segarra I, Roca M, Baliellas C, et al. Granulocyte-specific monoclonal antibody technetium-99m-BW 250/183 and indium-111 oxine-labeled leukocyte scintigraphy in inflammatory bowel disease. *Eur J Nucl Med* 1991;18:715–719.
17. Morguet AJ, Munz DL, Ivancevic V, et al. Immunoscintigraphy using technetium-99m-labeled antinca-95 antigranulocyte antibodies as an adjunct to echocardiography in subacute infective endocarditis. *J Am Coll Cardiol* 1994;23:1771–1778.
18. Becker W, Dölkemeyer U, Gramatzki MU, Schneider MU, Scheele J, Wolf F. Use of immunoscintigraphy in the diagnosis of fever of unknown origin. *Eur J Nucl Med* 1993;20:1078–1083.
19. Luig H, Eschner W, Bähre M, Voth E, Nolte G. Eine iterative Strategie zur Bestimmung der Quellenverteilung bei der Einzelphotonen-Tomographie mit einer rotierenden Gammakamera (SPECT). *Nuklearmedizin* 1988;27:140–146.
20. Bathmann J, Moser E. Vergleich von Skelettszintigraphie und Knochenmarksszintigraphie beim Nachweis ossärer Metastasen. *Radiologe* 1995;35:8–14.
21. Munz DL. Knochenmarkszintigraphie Prinzipien, klinische Ergebnisse und Indikationen. *Radiologe* 1992;32:485–494.
22. Reske SN, Karstens JH, Henrich MM, et al. Nachweis des Skelettbefalls maligner Erkrankungen durch Immunszintigraphie des Knochenmarks. *Nuklearmedizin* 1993; 32:111–119.
23. Bahk YW. *Combined scintigraphic and radiographic diagnosis of bone and joint diseases*. Berlin: Springer Verlag; 1994:47–49.
24. Lavender JP, Lowe J, Barker JR, Burn JI, Chaudhri MA. ^{67}Ga citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 1971;44:361–366.
25. Carroll B, Silverman PM, Goodwin DA, Dougall IR. Ultrasonography and indium-111 white blood cell scanning for the detection of intra-abdominal abscesses. *Radiology* 1981;140:155–160.
26. Knochel JQ, Koehler PR, Lee TG, Welch DM. Diagnosis of abdominal abscesses with CT, ultrasound, and indium-111 leukocyte scans. *Radiology* 1980;137:425–432.
27. Datz FL, Thorne DA. Cause, significance of cold bone defects on indium-111 labeled leukocyte imaging. *J Nucl Med* 1987;28:820–823.
28. Meller J, Conrad M, Behr T, Gratz S, Luig H, Becker W. Stellenwert der iterativen Rekonstruktion bei der Diagnostik von Leberhämangiomen. *Nuklearmedizin* 1997;36: 65–70.
29. Reuland P, Müller-Schauenburg W, Luig H, Eschner W, Feine U. Vergleich der klinischen Wertigkeit eines iterativen Rekonstruktionsverfahrens mit der gefilterten Rückprojektion bei der SPECT der Leber. *Nuklearmedizin* 1989;28:139–144.
30. Mok YP, Carney WH, Ferdinandez-Ulloa M. Skeletal photopenic lesions in indium-111 WBC imaging. *J Nucl Med* 1984;25:1322–1326.
31. Palestro CJ, Kim CK, Swyer AJ, Vallabhajosula S, Goldsmith SJ. Radionuclide diagnosis of vertebral osteomyelitis: indium-111-leukocyte and technetium-99m-methylene diphosphonate bone scintigraphy. *J Nucl Med* 1991;32:1861–1865.
32. Palestro C, Roumanas P, Swyer AJ, Chun KK, Goldsmith SJ. Diagnosis of muskuloskeletal infection using combined In-111 labeled leukocyte and ^{99m}Tc SC marrow imaging. *Clin Nucl Med* 1992;17:269–273.
33. Gratz S, Braun HG, Behr TM, et al. Photopenia in chronic vertebral osteomyelitis with technetium-99m antigranulocyte antibody (BW 250/183). *J Nucl Med* 1997;38:211–216.
34. Schauwecker DS. Osteomyelitis. Diagnosis with In-111-labeled leukocytes. *Radiology* 1989;171:141–146.
35. Saverymuttu SH, Maltby P, Batman P, Joseph AE, Maxwell D. False-positive localisation of indium-111 granulocytes in colonic carcinoma. *Br J Rad* 1986;59:773–777.