Diagnostic Significance of Indium-111 Granulocyte Scintigraphy in Febrile Patients

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Sixty-eight patients with fever of unknown origin, 32 patients with postoperative fever, and 26 patients with therapy-resistant fever after bacteremia were investigated with [^{111}In] granulocyte scintigraphy for the detection of abscesses. The results showed that the value of [^{111}In]granulocyte scintigraphy in the detection of infectious foci vary in these three types of febrile conditions. The overall sensitivity and specificity were 86.5% and 87.8%, respectively. We observed, however, a relatively low predictive value of a positive result in the fever of unknown origin group (73.1%), and also a low predictive value of a negative result in the bacteremia group (66.7%). The C-reactive protein (CRP) levels in patients with a true-positive scintigram were significantly ($p < 0.001$) higher than in patients with a true-negative scintigram. There was also a significant positive correlation ($p < 0.01$) between the serum CRP concentration and the intensity of the granulocyte accumulations. There was no correlation between the peripheral leukocyte count or the erythrocyte sedimentation rate (ESR) and the intensity of the granulocyte uptake. Therefore CRP, but not the leukocyte count or ESR, appears useful for selecting the patients who benefit most from granulocyte scintigraphy.

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Indium-111 (^{111}In) granulocyte scintigraphy has been found to be useful in the localization of bacterial abscesses and osteomyelitis (*1–4*). There are limitations, however, to the use of this method as evidenced by the quite frequent false-negative findings in chronic osteomyelitis (*3–5*) and occasional false-positive scintigrams. Peters and co-workers (*6*) investigated 101 patients and observed a specificity of 100%. Other investigators have also demonstrated the good specificity of the method, 90–98% (*1,2,7–9*). False-positive scintigrams have been caused by malignant processes such as intestinal cancer (*8*,10), bone metastases (*11*), and leukemic blast cell infiltration (*12*). Hematomas (*13*), bowel infarction, and bleeding (*14,15*) have also caused false-positive scintigrams. False-positive scintigrams due to cancer are evidently quite rare because Schell-Frederic et al. (*16*) observed only one patient with accumulation of granulocytes in a metastasis when investigating 117 patients with various malignancies.

The aim of this study was to evaluate the diagnostic usefulness of the [^{111}In]granulocyte scintigraphy in three important clinical conditions: fever of unknown origin not preceded by systemic infection or surgery during a period of 3 yr, postoperative fever, and therapy-resistant fever in patients with previous blood culture positive bacteremia.

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MATERIALS AND METHODS

Patients

One hundred twenty-six patients with febrile episodes suspected to be caused by bacterial processes were studied. The patients were divided into three subgroups. Sixty-eight patients had fever of unknown origin. The criteria for this group were: fever with maximum over 38°C lasting for at least 2 wk, negative blood and urine cultures, and routine laboratory tests and chest x-ray not revealing the cause of fever. This group consisted of 30 men and 38 women (mean age 45 yr; range 5–83 yr). Thirty-two patients were investigated because of postoperative fever (21 men and 11 women, mean age 53 yr; range 26–80 yr). Twenty-six patients had therapy-resistant fever subsequent to bacteriologically verified bacteremia defined as fever lasting over 1 wk and exceeding 38°C during appropriate antibiotic therapy (18 men and 8 women, mean age 53 yr; range 4–88 yr).

Laboratory Tests

The C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and peripheral blood leukocyte count were

studied using standard techniques in ~90% of the patients at the time of the scintigraphic examinations.

Granulocyte Labeling and Scintigraphy

Pure granulocytes were isolated and labeled with [^{111}In] oxine as described previously (*17*). Briefly, granulocytes were isolated from 40 ml venous blood anticoagulated with 10 ml acid citric dextrose. The erythrocytes were allowed to sediment at room temperature for 30–60 min (5–10 ml of hydroxyethyl starch was added, when ESR was below 50 mm/hr). The buffy-coat was centrifuged and the crude leukocyte-erythrocyte pellet was resuspended into 2 ml autologous plasma and centrifuged in a two-step discontinuous gradient made by mixing diluted iohexol and plasma. After centrifugation the granulocyte layer was aspirated, washed with saline, resuspended in 5 ml of room temperature saline after which 300–600 μCi [^{111}In]oxine was added. Thirty minutes later the free radioisotope was washed away and the granulocytes were resuspended in autologous plasma and injected intravenously. Greater than 99% of the labeled leukocytes were granulocytes and the cell suspension contained only few contaminating red cells and practically no platelets. Scintigraphy was performed on the following day with a large field gamma camera equipped with a medium-energy collimator.

Analysis of Scintigrams

Asymmetric accumulation of radioactivity in the scintigrams was considered a positive finding except for some very weak accumulations in the intestines and the oronasopharyngeal region, and weak accumulation of granulocytes caused by healing wounds, including various puncture sites. The intensity of the granulocyte uptake was graded as weak, moderate, or strong by subjective evaluation. A scintigram was considered "true positive" when the pathologic uptake was confirmed by surgery, biopsy, or autopsy. When morphological evidence could not be obtained, verification of "true positive" finding was based on other diagnostic procedures (laboratory tests, computed tomography, ultrasonography, standard x-ray, bone scans) in combination with clinically relevant signs and favorable response to antimicrobial medication. A positive scintigram was considered "false positive" when the finding was morphologically verified to be noninfectious or when no explanation could be found for the granulocyte uptake despite the use of several other diagnostic modalities. A scintigram was considered "true negative" when no infectious process was found during at least 3 mo of follow-up. A scintigram was considered "false negative" when an infectious process was found by other diagnostic procedures within 3 mo from the performance of scintigraphy.

Statistical Analysis

The linear correlation coefficient, Student's t-test, and the chi-square test for independence were used for statistical evaluation of results.

RESULTS

The results of the scintigraphic examinations are presented in Tables 1–3. Fifty-four patients had positive scintigrams. In 45 patients the findings were assessed as true positive. In nine patients scintigrams were considered false positive (17% of positive scintigrams). Negative scintigrams were obtained in 72 patients; seven patients had a false-negative finding. Sensitivity, specificity, and accuracy calculated from these data were 86.6%, 87.8%, and 87.3%, respectively.

TABLE 1
True-Positive (TP), True-Negative (TN), False-Positive (FP), and False-Negative (FN) [^{111}In]Granulocyte Scintigrams in Different Patient Categories

Patient category	n*	TP	TN	FP	FN
Fever of unknown origin	68	19 (28%)	40 (59%)	7 (10%)	2 (3%)
Fever after bacteremia	26	17 (65%)	6 (23%)	0 (0%)	3 (12%)
Postoperative fever	32	9 (28%)	19 (59%)	2 (6%)	2 (6%)
Total	126	45 (36%)	65 (52%)	9 (7%)	7 (6%)

* n = Number of patients.

Patients with Fever of Unknown Origin

Twenty-six patients (38%) had a positive scintigram, 19 patients had a true-positive result (18 verified, one considered as true positive on clinical grounds). Seven patients had a false-positive scintigram (37% of positive scintigrams). Forty-two patients had a negative scintigram; two were considered false negative. Sensitivity, specificity, and accuracy calculated from these data were 90.5%, 85.1%, and 86.8%, respectively. A scintigram from a patient with a large lung abscess is demonstrated in Figure 1.

Patients with Therapy-Resistant Fever After Bacteremia

Seventeen patients (65%) had positive scintigrams, all of which were true positive (14 verified, three considered as true positive on the basis of clinical course). Nine patients had negative scintigrams. Three of these patients were found to have infectious processes by other diagnostic means, and six were regarded as true negative. Sensitivity, specificity, and accuracy calcu-

TABLE 2
Sensitivity, Specificity, and Accuracy of [^{111}In]Granulocyte Scintigraphy in Different Patient Categories

Patient category	Sensitivity (%)	Specificity (%)	Accuracy (%)
Fever of unknown origin	85.1	90.5	86.8
Fever after bacteremia	85.0	100.0	88.5
Postoperative fever	81.8	90.5	87.5
Total	86.6	87.8	87.3

TABLE 3
Predictive Values of Positive and Negative [^{111}In] Scintigrams in Different Patient Categories

Patient category	% Predictive values	
	Positive scintigram	Negative scintigram
Fever of unknown origin	73.1	95.2
Fever after bacteremia	100.0	66.7
Postoperative fever	81.8	90.5
Total	83.3	90.3

lated from these data were 85.0%, 100%, and 88.5%, respectively.

Patients with Postoperative Fever

Eleven patients (34%) had positive scintigrams; nine were considered true positive (six verified, three considered true positive by clinical follow-up) and two were regarded as false-positive results (18% of positive scintigrams). Twenty-one patients had negative scintigrams, two of which were considered false negative. Sensitivity, specificity, and accuracy calculated from these data were 81.8%, 90.5% and 87.5%, respectively.

Correlation of Scintigraphy and Laboratory Test Results

The CRP values in patients with a true-positive scintigram were significantly higher ($p < 0.001$) than in patients with true-negative scintigrams. There was a significant correlation between the natural logarithm of the CRP values and the intensity of true-positive granulocyte accumulations ($r = 0.416$, $n = 42$, $p < 0.01$). The increase of the CRP level to over 60 mg/l increased the probability of a true positive scintigram from 18% to 43% (Fig. 2).

There was no statistically significant difference in ESR between true-positive and true-negative scintigrams (Fig. 3). Neither was there any statistically significant correlation between ESR and the intensity of true positive granulocyte accumulations.

There was no significant difference between the number of peripheral leukocytes in the patients with true positive and true negative scintigrams (Fig. 3). The leukocyte count did not correlate significantly with the intensity of true positive scintigrams.

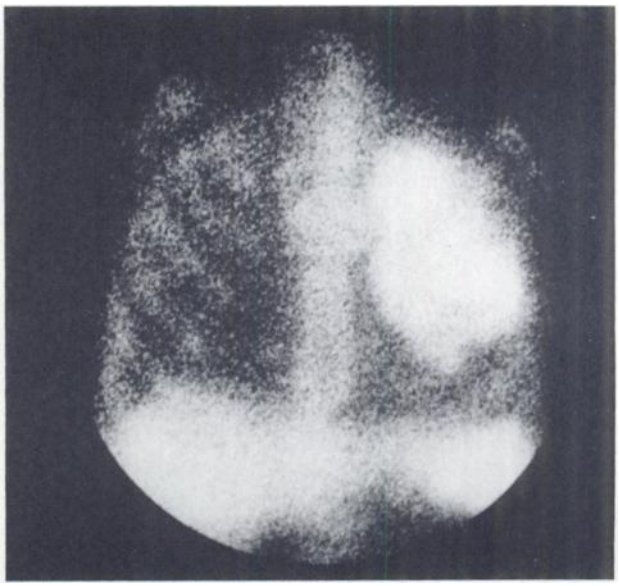

FIGURE 1
[^{111}In]granulocyte scintigraphy in a patient with fever of unknown origin. Previous standard chest x-ray was equivocal and an abscess elsewhere was suspected. Granulocyte scintigraphy revealed a large lung abscess proved by operation.

DISCUSSION

The overall sensitivity and specificity of [^{111}In]granulocyte scintigraphy were 86.5% and 87.8%, respectively. The sensitivity observed by us was therefore

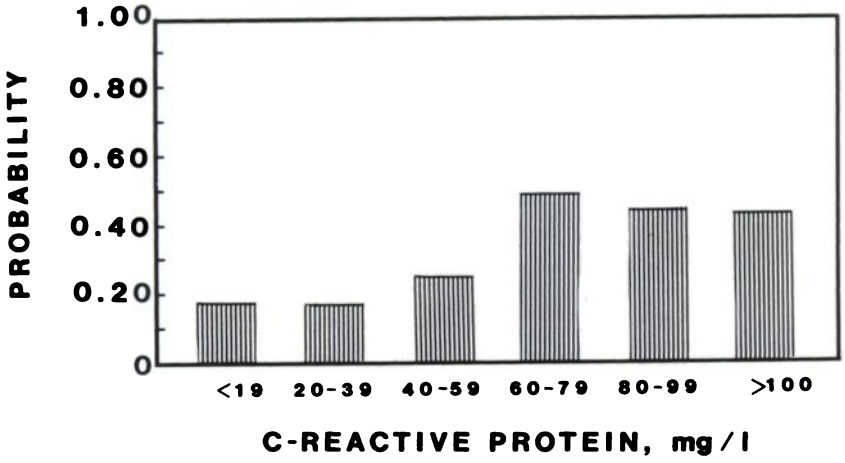

FIGURE 2
Association of probability of a true positive scintigram and CRP values.

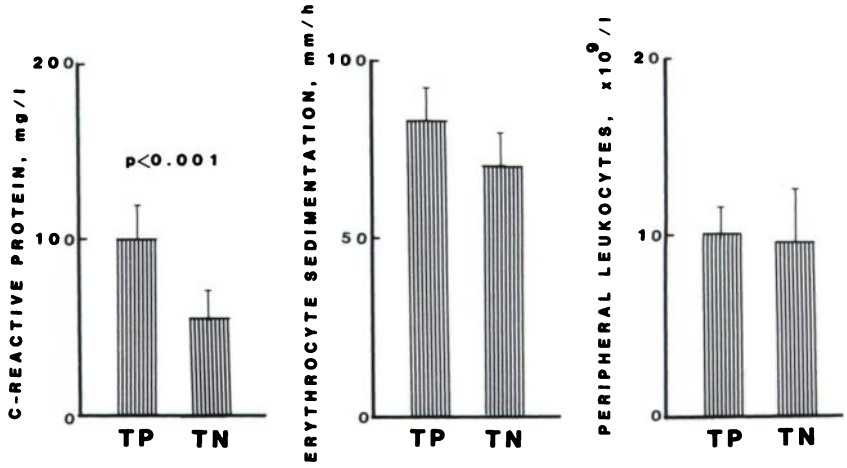

FIGURE 3
Laboratory test results in patients with true positive and true negative scintigrams (mean ± 2 s.e.m.).

similar to that reported by others (79–96%) (*1–3,6–9*). However, in our study a somewhat lower specificity was found than in some earlier reports (90%–100%) (*1–3,6–9*). The lower specificity observed by us was partly due to the more frequent occurrence of malignant processes visualized by [^{111}In]granulocyte scintigraphy (Table 4). False-positive results caused by bone metastasis and bowel malignancy (Fig. 4) have been reported also by others, but to our knowledge there is no previous report on a positive granulocyte scintigram caused by a sarcoma (hemangiopericytoma, Fig. 5). There were also three patients with radioactivity in the bowel causing false-positive scintigrams. In two patients, this conclusion was reached retrospectively on the basis of negative findings in CT and ultrasound, and absence of local symptoms. However, radiology or colonoscopy were not performed and therefore the exact etiology of the bowel uptake remained unknown, mild colitis being one possibility of high likelihood. In the third (Fig. 4) a diagnosis of adenocarcinoma in the sigmoid colon was verified by colonoscopy and subsequent operation; it is possible that the accumulation of granulocytes was not due to the carcinoma per se but to inflammatory reaction in the peritumoral area.

TABLE 4
False Positive [^{111}In]Granulocyte Scintigrams: Location of Uptake and Interpretation of Finding

Location of uptake	Diagnosis/interpretation
Pelvic bones	Adenocarcinoma
Heart	Retention of vascular radioactivity
Colon	Carcinoma
Right thigh	Hemangiopericytoma (sarcoma)
Right iliac fossa	Bowel radioactivity
Lungs	Accumulation of damaged cells
Multiple	Blast cell infiltrations*
Right iliac fossa	Bowel radioactivity
Right hip	Bone marrow radioactivity

* Previously reported (*12*).

The scintigraphy results varied significantly for the three patient groups (Table 1) studied when chi-square test was employed. The groups differed significantly when tested together ($p < 0.005$). When only two groups were compared at each time the bacteremia group differed significantly from the FUO group ($p < 0.001$) and the postoperative group ($p < 0.025$), whereas the FUO and postoperative groups did not vary significantly. Indium-111 granulocyte scintigraphy seems to be particularly useful in patients with therapy-resistant fever after bacteremia because more than every second scintigram (65%) was positive and there were no false positive results. However, the low predictive value of a negative scintigram (66.7%) hampers the reliability of the method in ruling out an infectious process in this group, although there are too few negative scans in this group for an ultimate conclusion. All the patients with therapy resistant fever after bacteremia and three out

FIGURE 4
A positive granulocyte scintigram caused by carcinoma in the sigmoid colon. In the ascending colon strong uptake for which no obvious explanation was found in colonoscopy or operation.

FIGURE 5
False-positive scintigram caused by hemangiopericytoma (sarcoma) in the right thigh.

of the four other patients with false negative scans had received systemic antimicrobial medication for at least 1 wk (Table 5), a fact that may be responsible, at least partly, for the high number of false-negative scintigrams. There were no significant differences in the number of patients receiving antimicrobial therapy in the different patient categories or in the number of patients with false-negative and true-positive scans. The spectrum of antibiotics used was too wide and the subgroups therefore too small for any safe conclusions concerning the effect of a single antibiotic. We also failed to detect some chronic infections, including two cases of chronic osteomyelitis. Although the number of positive scintigrams was high in the group with fever of unknown origin scintigraphy was less useful in this patient category because about every third positive scintigram was falsely positive. In this group granulocyte scintigraphy revealed three previously undetected malignancies showing the benefits of unspecific findings in certain patients. Importantly, in this group an infectious process could often be ruled out by scintigraphy (negative predictive value 95.2%).

TABLE 5
False-Negative [^{111}In]Granulocyte Scintigrams

Patient category	Final diagnosis	Antibiotics
Bacteremia	Tuberculous spondylitis	+*
Bacteremia	Chronic osteomyelitis	+
Bacteremia	Pneumonia	+
Postoperative fever	Chronic osteomyelitis	+
Postoperative fever	Intra-abdominal abscess	+
FUO	Periappendicular abscess	–†
FUO	Chronic cholecystitis	+

* Patient receiving antibiotics at time of scintigraphy.
† Patient not receiving antibiotics.

Of the laboratory tests studied CRP was the most useful in predicting a positive scintigram. A value over 60 mg/l predicted a positive scintigram in 43% of the cases, whereas a value below 60 mg/l decreased the probability of a positive scintigram to 18%. There was also a significant correlation between the CRP value and the intensity of the granulocyte uptake. Our results therefore indicate that CRP reflects to some extent the chemotactic activity of a local inflammatory process. ESR and peripheral blood leukocyte counts are of little or no value in predicting positive scintigrams.

In conclusion, our results show that [^{111}In]granulocyte scintigraphy is a useful method for localizing bacterial foci although its sensitivity and specificity vary in different categories of febrile patients. Of the standard laboratory tests studied only CRP seems to be of value for selecting patients who benefit most from [^{111}In] granulocyte scintigraphy, as judged by the probability of a positive finding.

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