

Diagnostic Value of ^{111}In -Granulocyte Scintigraphy in Patients with Fever of Unknown Origin

Andreas Kjaer, MD, PhD, DMS¹; and Anne-Mette Lebech, MD, PhD²

¹Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; and ²Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

^{111}In -granulocyte scintigraphy is often used as a diagnostic tool in patients with fever of unknown origin (FUO). However, its diagnostic performance has been studied in only a limited number of investigations, with most having been published more than 10 y ago; in addition, a broad range of sensitivities and specificities has been reported. Therefore, the aim of this study was to investigate the diagnostic value of granulocyte scintigraphy in patients fulfilling the criteria of FUO. Also studied was whether increased peripheral leukocyte count or C-reactive protein (CRP) level could be used to select patients for scintigraphy to raise the diagnostic value. **Methods:** For 31 patients with true FUO who underwent granulocyte scintigraphy at a third-line referral hospital between 1995 and 2000, the files and scintigraphy findings were reviewed retrospectively to test the ability of scintigraphy to identify infection or chronic inflammatory bowel disease as the cause of FUO. In addition, leukocyte counts and CRP values were recorded. **Results:** Scintigrams were true-positive in 6 cases, false-positive in 4 cases, true-negative in 19 cases, and false-negative in 2 cases. Sensitivity was 75%, specificity was 83%, the predictive value of a scintigram showing positive findings was 60%, and the predictive value of a scintigram showing negative findings was 90%. Leukocyte counts did not differ between patients with true-positive and true-negative scintigrams. In contrast, CRP was elevated in all patients with true-positive scintigrams but in only half the patients with true-negative scintigrams. However, if only patients with elevated CRP were used for calculation of test performance, the test performance was not improved. **Conclusion:** ^{111}In -granulocyte scintigraphy seems to have a reasonable sensitivity and specificity in cases of FUO, when one takes into account that ^{111}In -granulocyte scintigraphy is not a first-line test. The high predictive value of a scintigram showing negative findings may be especially valuable for ruling out an infectious cause of FUO. Neither peripheral leukocyte count nor CRP levels seem useful for selection of patients on whom scintigraphy should be performed.

Key Words: fever of unknown origin; granulocyte scintigraphy; leukocyte scintigraphy

J Nucl Med 2002; 43:140–144

Scintigraphy using ^{111}In -granulocytes is a well-established imaging technique for visualization of infection and chronic inflammatory bowel disease. Used for suspected intraabdominal abscess, osteomyelitis, vascular prosthesis infection, or chronic inflammatory bowel disease, ^{111}In -granulocyte scintigraphy has a high sensitivity and specificity (1,2). However, granulocyte scintigraphy is often performed on patients with fever of unknown origin (FUO), which is defined as more than 3 wk of illness with fever higher than 38.3°C documented on several occasions and no diagnostic clue despite 1 wk of intensive inpatient investigation (3). The diagnostic value of ^{111}In -granulocyte scintigraphy in this context is disputed and less well documented. Previous studies have reported highly variable sensitivities of 55%–85% and specificities of 74%–94% for detection of infection as the cause of FUO (4–7). However, all these studies were published more than 10 y ago, and the causes of FUO and their relative importance may have changed over the years (8). The differences could in part be caused by the introduction of various new and sensitive tests that may find the cause in many of the cases previously defined as FUO. Therefore, the aim of this study was to evaluate the diagnostic value of ^{111}In -granulocyte scintigraphy in a modern population of patients strictly fulfilling the criteria of FUO. In addition, we studied the possible use of leukocyte count or C-reactive protein (CRP) levels to increase the diagnostic performance of the scintigraphy.

MATERIALS AND METHODS

All ^{111}In -granulocyte scintigraphy examinations performed at the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Copenhagen, Denmark (a third-line referral university hospital), over a 6-y period (1995–2000) were reviewed retrospectively ($n = 189$). Thirty-eight of these scans were performed under the diagnosis of FUO. All of these cases were carefully reviewed by the authors to establish whether the criteria for FUO were fulfilled at the time of referral. Of the 38 cases, 31 (82%) fulfilled the criteria for FUO, that is, at least 3 wk of fever documented on several occasions and reaching 38.3°C without any diagnostic clue despite 1 wk of intensive inpatient investigations (3). The remainder of the analysis was performed on the 31 cases

Received Jul. 23, 2001; revision accepted Oct. 22, 2001.

For correspondence or reprints contact: Andreas Kjaer, MD, PhD, Department of Clinical Physiology and Nuclear Medicine, Section 4011, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.

E-mail: kjaer@mfi.ku.dk

of true FUO (17 females, 14 males; age range, 13–71; mean age, 40 y). Leukocyte counts and CRP levels were measured in the same week that the scintigraphy was performed.

¹¹¹In-Granulocyte Scintigraphy

Autologous granulocytes were labeled with ¹¹¹In-tropolone. In brief, 50 mL venous blood were drawn and prevented from coagulating with 7.5 mL citric acid–glucose. The erythrocytes were allowed to sediment at room temperature for 30–60 min. Cell-rich plasma was then transferred to another tube, and granulocytes were isolated by gradient centrifugation. Isolated granulocytes were resuspended in 1 mL cell-free plasma and added to a mixture of 20–30 MBq ¹¹¹InCl₃ and 0.1 mL 0.0044 mol/L tropolone. After centrifugation, resuspension, and quality control, a dose of 9–12 MBq labeled granulocytes was injected intravenously. Labeled granulocytes were injected within 1 h after labeling.

For all patients, anterior and posterior planar images of the whole body were obtained 20–24 h after injection of labeled granulocytes using a gamma camera (Millennium or XRT; General Electric Medical Systems, Milwaukee, WI) with a medium-energy general-purpose collimator. Counts were acquired for 10 min in two 20% windows centered at 171 and 245 keV.

Analysis of Scintigrams

Two physicians routinely reviewed all scintigrams at the time they were performed. These routine reviews were primarily used because they reflected the diagnostic value in everyday routine. However, all scintigrams were also reviewed by the authors, and in only 1 case was there any discrepancy. In that case, an equivocal finding was changed to a negative one, which was then used in the further analysis. The diagnostic value of ¹¹¹In-granulocyte scintigraphy was evaluated by its ability to identify an infectious cause of FUO or chronic inflammatory bowel disease as the cause of FUO. Thus, a scintigram was considered true-positive when an infectious focus identified by scintigraphy was later verified by another method (surgery, biopsy, other imaging modalities). Scintigrams identifying foci that were never verified during follow-up or foci that were verified as noninfectious were considered false-positive. Cases in which scintigraphy identified infectious foci that were later verified but were not the cause of fever were also considered false-positive. A scintigram was considered true-negative when no infectious process was found during follow-up, that is, also if the cause of FUO was never established. Scintigrams were considered false-negative if an infectious focus was identified by another method and considered to be the cause of FUO. A favorable response to antibiotic therapy in patients with no scintigraphic focus also indicated a false-negative scintigram.

Statistical Analysis

The proportion of elevated leukocyte counts and CRP levels in the scintigraphic groups was compared by the χ^2 test. $P < 0.05$ was considered significant.

RESULTS

Of the 31 patients studied, a final diagnosis was obtained in 22 (71%). In 8 (26%), an infectious focus or chronic inflammatory bowel disease was considered the cause of FUO (Table 1). Of the 14 patients whose condition had a noninfectious cause that received a final diagnosis, the

TABLE 1
Infection or Chronic Inflammatory Bowel Disease
as Cause of FUO

Condition	No. of patients
Vertebral osteomyelitis*	1
Leptospirosis*	1
Infected hemodialysis catheter placed in superior vena cava†	1
Pyelonephritis†	1
Diverticulitis (<i>Salmonella dublin</i>)†	1
Abdominal abscess†	1
Crohn's disease†	2

*Not identified on false-negative scintigram.
†Identified on true-positive scintigram.

causes were neoplasms (3 patients), Still's disease (3 patients), cerebrally triggered fever (3 patients), lung embolism (1 patient), subacute thyroiditis (1 patient), polymyalgia rheumatica (1 patient), other connective tissue disease (1 patient), and hematoma fever (1 patient). In 9 patients, no cause was found, and most of these (6 patients) spontaneously recovered and had no fever at the end of follow-up. In the remaining 3 patients, fever still prevailed at the end of follow-up, but an infectious cause was found to be unlikely. Of the patients whose condition had an infectious cause, the scintigrams were (true) positive in 6 (75%) and (false) negative in 2 (25%). Examples of true-positive scintigrams are shown in Figures 1–3. Of the 23 patients whose condition had a noninfectious cause, scintigrams were (true) negative in 19 (83%) and (false) positive in 4 (17%). The foci of the false-positive scintigrams are listed in Table 2.

In this study, sensitivity was 75% (6/8), specificity was 83% (19/23), the positive predictive value (PPV) of a scintigram with positive findings was 60% (6/10), and the negative predictive value (NPV) of a scintigram with negative findings was 90% (19/21).

Twelve patients (39%) had an increased leukocyte count, and 22 patients (71%) had increased levels of CRP. There were no differences in the proportion of patients with an increased leukocyte count between the group with true-positive scintigrams and the group with true-negative scintigrams (Table 3). In contrast, all patients with true-positive scintigrams had elevated CRP levels, whereas only half the patients with true-negative scintigrams had elevated CRP levels. If only the 22 patients with elevated CRP levels were used for calculation of test performance, the sensitivity was 75% (6/8), the specificity was 71% (10/14), the PPV was 60% (6/10), and the NPV was 83% (10/12).

DISCUSSION

In our study, 38 patients with a diagnosis of FUO were referred for ¹¹¹In-granulocyte scintigraphy. However, when files were carefully reviewed, almost 20% of the patients did not fulfill the criteria for this diagnosis. This fact under-

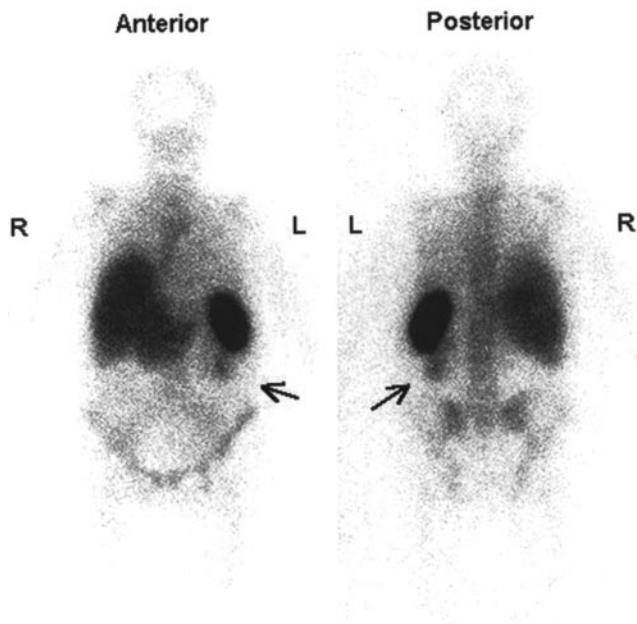


FIGURE 1. True-positive scintigram shows left-sided pyelonephritis (arrows) as cause of FUO.

scores the importance of a careful definition of FUO and a careful review of cases when those cases are used to establish the diagnostic value of a test investigating FUO.

A cause of FUO was found in only 71% of our patients, thus leaving a substantial group undiagnosed with regard to cause. In general, this rate is in agreement with several other

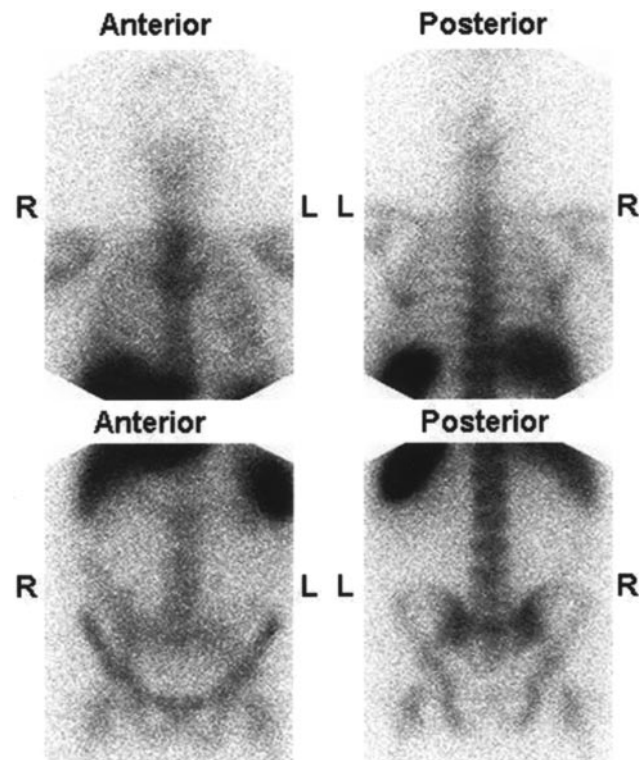


FIGURE 3. True-positive scintigram shows diverticulitis in transverse and descending colon as cause of FUO.

studies (9). In 2 such retrospective studies, the percentages of patients for whom no cause of FUO was found were 26% and 30% (10,11). In a recent prospective study in which the criteria of FUO were changed slightly, no cause of FUO was established in 30% of the patients (12). It could be argued that the high percentage of patients with an undiagnosed cause of FUO in our study was caused by insufficient follow-up. However, we followed up all patients for at least 12 mo. Furthermore, two thirds of the patients for whom no cause of FUO was established recovered spontaneously, and extending the follow-up of this group would have been unlikely to show any cause of FUO. In patients for whom a diagnosis was obtained, the distribution of causes was similar to that found in other studies; that is, infection, collagen-vascular disease, and neoplasms were the major groups. However, the number of patients for whom malignant disease was diagnosed as the cause of FUO was small in our

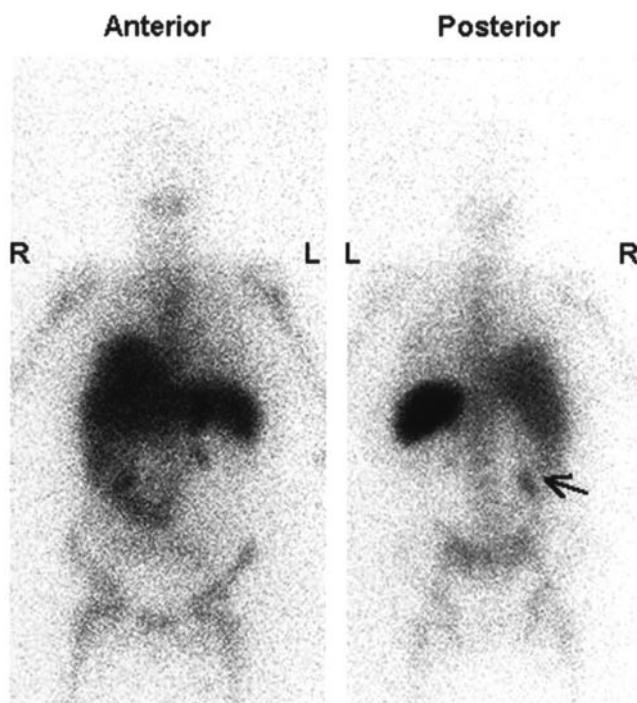


FIGURE 2. True-positive scintigram shows abdominal abscess (arrow) as cause of FUO.

TABLE 2
False-Positive ¹¹¹In-Granulocyte Scintigraphy Findings

Finding	No. of patients
Maxillary sinusitis; confirmed and treated but not cause of FUO	2
Cold spot in vertebral column; multiple embolisms cause of FUO	1
Accumulation in 1 hand; rheumatoid arthritis cause of FUO	1

TABLE 3

Patients with Increased Leukocyte Count or CRP Level According to Scintigraphic Results

Scintigraphy	Elevated leukocyte count	Elevated CRP level
True-positive (<i>n</i> = 6)	3 (50%)*	6 (100%) [†]
False-positive (<i>n</i> = 4)	3 (75%)	4 (100%)
True-negative (<i>n</i> = 19)	5 (26%)	10 (53%)
False-negative (<i>n</i> = 2)	1 (50%)	2 (100%)

*Not statistically significant.

[†]*P* < 0.05 vs. true-negative (χ^2 test).

study, compared with earlier studies, but not in comparison with 1 recent investigation (10). Because the causes of FUO and their relative importance may have changed over the years (8), comparison with more recent studies seems most relevant. The fact that we found only a few neoplasms could have been caused by the improved diagnostic tests for cancer, leaving fewer of these patients in the group classified as having FUO. In addition, the low rate of neoplasms also documents that the investigations performed on patients before referral were indeed intensive and in accordance with our hospital being a third-line referral hospital. We believe that our study population, taken together, is representative of the typical FUO population encountered today.

We found a sensitivity of 75% and a specificity of 83% for ¹¹¹In-granulocyte scintigraphy when used in patients with FUO. In general, these values agree with those found in previous studies. The largest previously published study, with 68 patients, found a sensitivity of 85% and a specificity of 91% (4). In another study, with 32 patients, a sensitivity of 73% and a specificity of 94% were found (7), whereas yet another study, with 28 patients, found a sensitivity of 60% and a specificity of 78% (6). Two additional studies on the diagnostic performance of ¹¹¹In-granulocyte scintigraphy have been reported (5,13) but are not directly comparable with the previously mentioned studies and ours. In 1 of these 2 additional studies (13), in which granulocyte scintigraphy was compared with sonography, diagnostic performance was measured as the ability to show any cause of FUO, that is, a scintigram with negative findings in a patient for whom the cause of FUO is later shown to be neoplastic was considered false-negative. We, in accordance with the principles used in most studies, do not consider this method of judging the performance of ¹¹¹In-granulocyte scintigraphy to be fair, because this method implies that ¹¹¹In-granulocyte scintigraphy should be used as a first-line screening test. In the other study (5), repeated (negative) scans of the same patients were included, making the performance of the test irrelevant for the typical clinical setting, namely first-time referral for scintigraphy as part of an investigation of FUO. Our study, taken in concert with the

previous published studies, indicates a sensitivity of approximately 80% and a somewhat higher specificity.

Is this a high diagnostic performance? For many types of tests, performances in this range would make the test obsolete, for example, if the test was used for screening or as a first-line test. However, the use of ¹¹¹In-granulocyte scintigraphy in FUO is special, because the test typically is used at a late stage when several other tests have been performed. Used in this way, the pretest probability of an infectious cause is high, typically 20%–40%, and the performance of the test seems sufficient to justify its use. Thus, in our study, we found a PPV of 60% and an NPV of 90%, indicating that negative scintigraphy findings almost rule out an infectious cause. The high NPV has been confirmed in other studies, in which the NPV was found to be 95% and 90% in populations in which the cause of FUO was infection in 31% and 25% of the patients, respectively (4,6). In the same 2 studies, the PPV was comparatively low, namely 73% and 38%, respectively (4,6). Contrasting with these data, 1 study found a PPV of 89% and an NPV of 84% in a population in which 35% of the patients had an infectious cause of FUO (7). It seems that, in general, negative scintigraphy findings have a high predictive value, whereas the predictive value of positive scintigraphy findings is low. Because predictive values depend on the prevalence of infectious causes, the values are comparable only if the different studies are undertaken in comparable populations. Indeed, the proportions of infection as the cause of FUO in the above-described studies were in the same range.

A discussion of whether ¹¹¹In-granulocyte scintigraphy is the best radionuclide method in patients with FUO is beyond the scope of this article. However, the use of ¹⁸F-FDG PET seems promising in these patients (14).

Some have speculated that the degree of leukocytosis or the level of the acute-phase reactant CRP could be used to select FUO patients who should be referred for ¹¹¹In-granulocyte scintigraphy to increase the diagnostic performance of the test. We found no difference in leukocyte counts between patients with true-positive and true-negative scintigrams. This finding is in accordance with results found by others (4,6). Furthermore, sensitivity, specificity, and accuracy were calculated to be similar in patients with and without elevated leukocyte count (5). In contrast, previously, higher levels of CRP were found in patients with true-positive scintigrams than in patients with true-negative scintigrams (4). Our study confirmed this observation, because all patients with true-positive scintigrams had elevated CRP levels, whereas only half the patients with true-negative scintigrams had elevated levels. However, because all patients with false-positive scintigrams also had elevated CRP levels, the diagnostic performance was not improved if only patients with elevated CRP were included. Therefore, neither leukocyte count nor CRP level seems to be of any value in selection of patients suited for ¹¹¹In-granulocyte scintigraphy.

CONCLUSION

¹¹¹In-granulocyte scintigraphy seems to have a reasonable sensitivity and specificity in cases of true FOU when one considers that the test is not a first-line or screening test but adjunctive in selected cases. The high predictive value of negative scintigraphy findings may be especially valuable for ruling out an infectious cause of FOU. Neither peripheral leukocyte count nor CRP level seems a useful guide as to which patients should be referred for scintigraphy.

ACKNOWLEDGMENT

Secretarial assistance by Philip Junker is gratefully acknowledged.

REFERENCES

1. Datz FL. Indium-111-labeled leukocytes for the detection of infection: current status. *Semin Nucl Med.* 1994;24:92–109.
2. Forstrom L. Indium-111 labeled leukocyte imaging in the diagnosis of infection and inflammatory disease. In: Henkin RE, Boles MA, Dillehay GL, et al., eds. *Nuclear Medicine.* St. Louis, MO: Mosby; 1996:1619–1635.
3. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine.* 1961;40:1–30.
4. Syrjala MT, Valtonen V, Liewendahl K, Myllyla G. Diagnostic significance of indium-111 granulocyte scintigraphy in febrile patients. *J Nucl Med.* 1987;28:155–160.
5. MacSweeney JE, Peters AM, Lavender JP. Indium labelled leucocyte scanning in pyrexia of unknown origin. *Clin Radiol.* 1990;42:414–417.
6. Davies SG, Garvie NW. The role of indium-labelled leukocyte imaging in pyrexia of unknown origin. *Br J Radiol.* 1990;63:850–854.
7. Schmidt KG, Rasmussen JW, Sorensen 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.
8. Barbado FJ, Vazquez JJ, Pena JM, Arnalich F, Ortiz-Vazquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. *Postgrad Med J.* 1992;68:884–887.
9. Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet.* 1997;350:575–580.
10. Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. *Arch Intern Med.* 1992;152:51–55.
11. de Kleijn EM, van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. *Neth J Med.* 1995;47:54–60.
12. de Kleijn EM, Vandenbroucke JP, van der Meer JW, for the Netherlands FUO Study Group. Fever of unknown origin (FUO). I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. *Medicine (Baltimore).* 1997;76:392–400.
13. Tudor GR, Finlay DB, Belton I. The value of indium-111-labelled leucocyte imaging and ultrasonography in the investigation of pyrexia of unknown origin. *Br J Radiol.* 1997;70:918–922.
14. Blockmans D, Knockaert D, Maes A, et al. Clinical value of [(18)F]fluorodeoxyglucose positron emission tomography for patients with fever of unknown origin. *Clin Infect Dis.* 2001;32:191–196.

