Evaluation of ^{111}In Leukocyte Whole Body Scanning

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Indium-111 oxine, polymorphonuclear cells isolated and labeled with ^{111}In were used for studying abscesses and inflammatory conditions. There were 64 total scans done in 59 patients, 32 male and 27 female, aged 3-81 years (average, 51). The original clinical diagnosis was abscess in 33 patients. The whole blood cell scan was abnormal in 12 (36%) of these, and a good clinical correlation was obtained in 11 of the 12. In the 21 with a normal scan, 18 had no evidence of abscess, yielding one false-positive and three false-negative interpretations in the abscess group. Thirteen patients had fever of unknown origin, nine had negative scans and no subsequent evidence of abscess, and four had positive scans with good correlation in three. Acute bone and joint infections were positive on scan (4/4), whereas chronic osteomyelitis was negative (0/2). Three patients with acute myocardial infarction and three of four with subacute bacterial endocarditis had normal scans. All three studies in renal transplant rejection showed positive uptake in the pelvic kidneys. Indium-111 white blood cell scans have proved useful to diagnose or exclude a diagnosis of abscess or inflammatory condition infiltrated with polymorphonuclear leukocytes.

Occult abscesses cause toxemia, septicemia, and, if untreated, death. Occasionally, abscess diagnosis is clinically difficult and appropriate treatment delayed. In severely ill and compromised patients, symptoms and signs due to a septic focus might be ascribed to the underlying disease, or its treatment; alternatively, clinical features may be blamed on an abscess where none exists. Intraabdominal abscess is a potential complication of abdominal surgery, especially when the peritoneum has been soiled. The resulting pelvic or subphrenic abscesses may not be diagnosed and treated expeditiously. Therefore, early diagnosis of abscess is very important, but accurate knowledge of its location is equally important since drainage is usually the treatment of choice.

For many years, the possibility of using labeled polymorphonuclear leukocytes to localize abscesses was discussed [1-5]; however clinical usefulness of this approach was thwarted by lack of a suitable gamma-emitting label. The work of McAfee, Thakur, and others [6-8] in 1976 and 1977 demonstrated conclusively that leukocytes can be labeled efficiently with ^{111}In and retain their functional capabilities of host defense against pyogenic infections. Therefore, in theory, ^{111}In leukocytes provide a specific homing marker to label abscesses or other inflammatory conditions associated with leukocyte accumulations. There are reports of the value of this test in small numbers of patients [9, 10]. We show how easy the test is to conduct and discuss the results of whole body ^{111}In white blood cell scans in 59 patients.

Subjects and Methods

There were 64 total whole body ^{111}In white blood cell scans done in 59 patients. There were 27 female patients, aged 17-81 years (average, 51), and 32 male, aged 3-79 years (average, 51). Informed written consent was obtained for all patients. Initial clinical problems comprised possible abscess or a mass lesion suspicious for abscess or tumor. In 60

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studies, autologous white blood cells were labeled. Because of granulocytopenia at the time of scanning, donor cells were used in the other four studies.

The method of labeling the cells, adapted from Thakur [8], uses 40 ml venous blood added to 500 U preservative-free heparin, 3 ml hydroxyethylstarch (Hetastarch, McGraw Labs., Chicago, Ill.) and 3 ml physiological nonbacteriostatic saline in a sterile polyethylene tube. One-half of these quantities were used for children. The mixture sat for 1 hr, allowing the red blood cells and some of the lymphocytes to sediment by gravity, leaving a platelet- and polymorphonuclear-rich supernatant [11]. The supernatant was removed and centrifuged at $\times 250$ *g* for 5 min to form a white blood cell pellet. The platelet-rich plasma was removed and spun at $\times 1,000$ *g* for 30 min to produce platelet-free plasma that was used for resuspension of the labeled cells just before reinjection into the patient. The white blood cell button was resuspended in 5 ml saline and 1 mCi of ^{111}In oxine in 50 μl ethanol and 150 μl saline was added drop by drop with gentle swirling of the cells. The cells and radiopharmaceutical (Diagnostic Isotopes, Inc., Bloomfield, N.J.) were incubated for 30 min at room temperature and then centrifuged at $\times 250$ *g* to form a button of labeled cells. The radioactivity in the supernatant and in the white blood cells were counted and the efficiency of the labeling calculated. Usually this was 75%–95% (750–950 μCi of ^{111}In). The white blood cells were gently resuspended in 5–10 ml of platelet-poor plasma and reinjected with minimal delay. The separation and labeling of white blood cells took about 2 hr and could be achieved efficiently by each of our nuclear medicine technologists.

Whole body scans were made 18–24 hr later, using either a Picker Dyna 4 camera with moving table or a Searle tomographic scanner. In patients with more than one drainage tube or in those requiring assisted ventilation, the scan was constructed from a series of spot views.

Each patient's chart was reviewed retrospectively and the result of the scan was compared with operative findings, results of other diagnostic tests, and final discharge diagnosis. Since many of the patients had serious underlying illnesses, they were often readmitted and follow-up information was available.

Definitions

True positive. Scan abnormal and abscess found at that site at operation.

True negative. Scan normal and no abscess found at operation. Since a negative scan frequently dissuaded the surgeon from operating, patients without evidence of abscess on other tests, who were not treated with antibiotics, and who did not have a discharge diagnosis of abscess were included in this group.

False positive. Focal uptake of radioactivity on scan, but no abscess found at operation.

False negative. Negative scan but abscess found at surgery or diagnosed by other technique (e.g., ultrasound plus needle aspiration).

Sensitivity. true-positive ratio (number of patients with abnormal test divided by total number of patients with disease).

Specificity. true-negative ratio (number of patients with normal test divided by total number of patients without disease).

Results

Table 1 shows the outcome of the ^{111}In white blood cell scans compared with the patients' clinical conditions and whether the scans correlated well with the final diagnoses. Figure 1 shows the normal distribution of ^{111}In white blood cells and figure 2 is a scan of a patient with an abdominal abscess. Of 33 patients referred with suspected abscess, scans were positive in 12 (36%); an abscess was found in 10. Another patient had a positive scan showing diffuse uptake in the heart that could not have been attributed to blood pool activity. A diagnosis of myocarditis was made, which was the final clinical diagnosis. The false-positive scan was due to increased accumulation in the thigh of a cardiac transplant recipient interpreted as an abscess. This lesion was subsequently proven to be histiocytic lymphoma.

Three of the 21 patients with scans interpreted as normal were found to have abscesses. Two of the abscesses were hepatic; one of these was sterile and *Candida* was cultured from the other. In the third patient, a pelvic abscess was found at operation 4 days after the negative scan. In retrospect, these scans still appear normal. There was no clinical evidence of abscess on other tests, at operation, or on follow-up in the other 18 patients.

In 13 patients referred with a diagnosis of fever of unknown origin, none had strong clinical evidence of abscess, but the test was done to either find one or exclude this diagnosis with some certainty. Scans were normal in nine of this group; none of these had a final diagnosis of abscess. In the four positive scans, two had lung uptake in sites of pneumonia and one had bowel uptake due to Crohn's disease. The last patient, who was injected with donor cells, had impressive accumulations of radioactivity in the abdomen in the regions of the splenic flexure and pancreas. He had recently had his spleen removed for Felty's syndrome and abscesses seemed a strong possibility based on the scan appearance. The patient refused additional investigations and was lost to follow-up.

Positive uptake of ^{111}In white blood cells was noted in all four patients with acute osteomyelitis or septic arthritis at the site of pathology. Both patients with chronic osteomyelitis had normal white blood cell scans, whereas ^{99m}Tc methylene diphosphonate scans were abnormal. None of the three patients with acute myocardial infarction had positive white blood cell scans, even though spot views were made over the precordium, and only one of four patients with subacute bacterial endocarditis had a positive scan, which did not show intense uptake.

Seven patients had solid cancers, and, other than the patient with histiocytic lymphoma of the thigh, no cancer case showed positive uptake of labeled white blood cells. In fact, in one patient, hepatic metastases showed as photon-deficient areas. In another, ^{99m}Tc bone scan and ^{67}Ga scans of the same areas of the femurs had been positive. The lesions were found to be adenocarcinomas and, despite extensive workup, the site of primary tumor was not found.

Discussion

The diagnosis of abscess has depended on a constellation of clinical, hematologic, bacteriologic, and radiologic tests. Although blood studies may indicate that a septic focus is present, they give no information about the site of infection. Fluoroscopy might show an elevated immobile diaphragm

TABLE 1: **Scanning Results**

Clinical Condition	No. Patients Studied	No. Positive	No. True Positive	No. Negative	No. True Negative
Suspected abscess	33	12	11	21	18
Fever of unknown origin	13	4	3	9	9
Acute bone or joint infection	4	4	4	0	...
Chronic bone infection	2	0	...	2	?2
Subacute bacterial endocarditis	4	1	*	3	*
Renal transplant	3	3	*	0	...
Myocardial infarct	3	0	...	3	*
Felty's syndrome	2	0	...	2	*
Total	64	24	...	40	...

* It is still too early to definitively state whether or not scanning results are correct for these conditions.

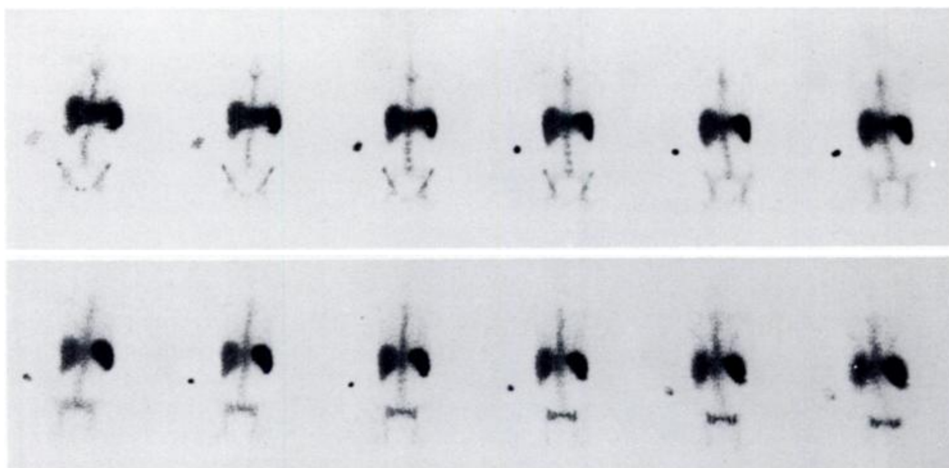

Fig. 1.—Tomographic scan of normal distribution of ^{111}In (1 mCi) leukocytes in 34-year-old woman 20 hr after injection. Top left image most anterior; each successive image 2 cm deeper; bottom right image most posterior. Labeled cells in liver, spleen, and bone marrow. Clinically, abscess was suspected; scan was normal and no abscess was found at laparotomy.

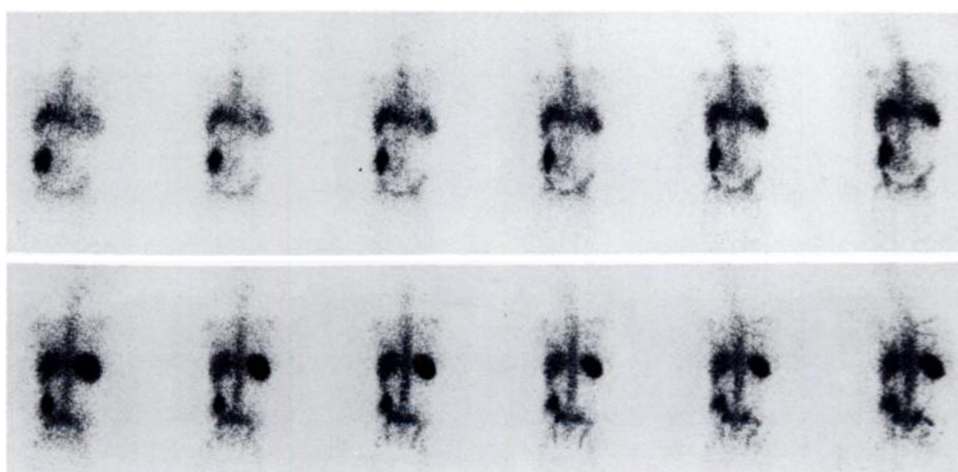

Fig. 2.—Tomographic scan about 20 hr after intravenous injection of 600 μCi ^{111}In leukocytes in 42-year-old man. Intense accumulation in right side of abdomen proved to be abscess. Small area of uptake in left buttock on bottom right image was site of recent intramuscular injection.

due to a subphrenic abscess. Three tests currently used for abscess detection, ultrasound, computed tomography (CT) and ^{67}Ga scanning, have had varying success. Ultrasound shows a fluid-filled mass lesion containing debris surrounded by an inflammatory capsule [12]. Although some studies conclude that ultrasound provides a test of high specificity and sensitivity [12], other investigators have found it less useful [13, 14]. False-positive results have been reported [15]. Computed tomography (CT) also diagnoses fluid collections with a high degree of accuracy and can prove unequivocally whether or not gas is intralesional. With CT, diagnostic accuracy has also varied considerably

[14, 16, 17]. Gallium-67, originally used as a tumor scanning agent [18], was also found to localize in inflammatory disorders, including abscesses, and there is now considerable information about its usefulness in abscess detection [19-23]. Although ^{67}Ga is very valuable, it has several drawbacks. It labels both tumors and abscesses, and, therefore, lacks specificity. A considerable amount of the injected material is excreted through the gut, usually about 10%, but on occasion as much as 37% [24]. Therefore, considerable caution must be exercised in evaluation of abdominal collection of ^{67}Ga. The slow blood clearance of ^{67}Ga and the four energy peaks of its gamma emissions are added problems.

We address the clinical value of ^{111}In leukocytes in detection of abscesses, or inflammatory conditions associated with infiltration of polymorphonuclear leukocytes. The technique used to isolate the cells for labeling does not produce a uniform population of polymorphs, but it does exclude red blood cells, platelets, and a significant proportion of lymphocytes [11]. Many of the patients studied had a leukocytosis due to an increased proportion of polymorphs, thus increasing the selectivity of our cell population. In four patients with granulocytopenia, ABO typed blood from normal donors was used for cell preparation and labeling. Donor cells appeared functional. In two of these four patients, focal uptake of radioactivity was noted; in one, an abscess was proven; the other patient refused further tests. Patients with less than 2,000 polymorphs/mm^3 should probably be studied with labeled donor cells. Assuming less than 1 mCi ^{111}In-labeled polymorphonuclears are injected, the total body radiation dose is 0.2 rad; the spleen is the key organ receiving 5 rad.

The proposal to use labeled leukocytes to identify abscesses is not new; however, a suitable label has not been available until quite recently. Chromium-51 has been used successfully to study white blood cell kinetics [1, 2], and, although proposed for abscess detection [3, 4] this radionuclide is not well suited for imaging. Phosphorus-32 emits beta particles that cannot be imaged by external detectors, so it is used only for in vitro studies [25]. In diagnostic nuclear medicine, ^{99m}Tc is the most widely used radionuclide, but its physical half-life of 6 hr reduces its desirability for abscess detection.

Recent investigations [6, 7, 9, 10] illustrate the usefulness of ^{111}In, in the form of ^{111}In oxine, as a suitable radiopharmaceutical for labeling blood elements. In the case of polymorphs, about 75%-95% of the agent attaches to intracellular proteins and the physical half-life of 2.7 days and abundant 173 keV and 247 keV gamma rays are fairly well suited for whole body imaging 20-72 hr after injection. The results of scanning with ^{111}In-labeled white blood cells should be compared with those of ^{67}Ga. However, such a comparison is difficult since ^{111}In and ^{67}Ga have similar gamma energies and half-lives of about 3 days. These facts make it virtually impossible to compare scans within a period of less than 6 days, and, if the first study is positive for abscess, it is unlikely that the patient would be left untreated over this period of time. In animal studies, the ratio of ^{111}In in abscess to blood varied from 35-117 to 1, whereas ^{67}Ga ratios of abscess to blood were between 1.2:1 and 8:1 [26]. Recently, we compared the radioactivity from a draining fistula with blood radioactivity in a young man with an abdominal abscess and obtained a ratio of 27:1. (This patient is not part of the group under discussion.)

Labeled white blood cells are not excreted by normal kidney or bowel. As a result, abnormal accumulation of ^{111}In in the abdomen cannot be due to normal fecal concentration, which is an advantage over ^{67}Ga images. In addition recent surgical wounds show considerably more uptake of ^{67}Ga than ^{111}In white blood cells. Many malignant lesions concentrate ^{67}Ga [27], making differentiation from abscess difficult. It has been suggested that uptake of ^{67}Ga in abscess occurs early and scans at 6 hr are satisfactory [28]. However, the background activity of ^{67}Ga is high at that time, making interpretation somewhat difficult [17]. Also some tumors show early uptake of ^{67}Ga, and bowel activity has been encountered as early as 6 hr [29].

We reviewed 64 consecutive ^{111}In white blood cell scans. Good techniques for separation and labeling of the cells are important, but they are not difficult and could be introduced in most nuclear medicine facilities. The normal distribution of labeled polymorphs includes liver, spleen, and bone marrow (fig. 1). As stated above, none is excreted by kidney or bowel and uptake in these sites frequently indicates an abnormality. Although ^{111}In white blood cell scans are easier to interpret than ^{67}Ga scans, there are several important considerations. Because of normal uptake in liver and spleen, abscesses within these organs might be overlooked. Two hepatic abscesses in our series were not detected. One of the abscesses was sterile while the other was culture positive for *Candida*; it is probable that they did not concentrate a meaningful amount of polymorphs. Despite this, if a regular ^{99m}Tc sulfur colloid scan was superimposed on the ^{111}In scan, and an area of reduced uptake noted on ^{99m}Tc scan where ^{111}In distribution was normal, the interpretation of the white blood cell scan would be different. This subtraction technique has been found valuable for ^{67}Ga scans [30]. We suggest that this approach be adopted if there is clinical suspicion of upper abdominal abscess, or if hepatic or splenic lesions have been detected on CT or ultrasound.

Abnormal uptake that seems to be in the gut of patients with inflammatory diseases of the lips, sinuses, and esophagus should be interpreted with great caution. In these patients an exudate of labeled white blood cells passes from the lesions into the gut lumen and gives the appearance of a focal lesion in the abdomen, as well as sinuses, etc. A repeat scan after 24 hr can prove whether the radioactivity moves through the gut. We found it unnecessary to purge patients (as is done with ^{67}Ga scans), which is a considerable advantage for ill, toxic patients.

Our study did not routinely compare white blood cell scans with ultrasound and/or CT, although many patients had one or both of these tests. Using the final clinical diagnosis as the correct outcome, it is possible that we biased our true negative results because laparotomy was not done on most patients to prove there was no abscess. One patient had a false-negative scan for which we have no good explanation. The other patients with negative scans who did go to laparatomy or autopsy had no evidence of abscess. For the 51 studies for diagnosis of abscess, bone and joint infection, or fever of unknown origin for which we have follow-up information, the ^{111}In white blood cell scans had a specificity and sensitivity of 90%. In 1977, Thakur et al. [10] described focal accumulation in 12 of 15 patients studied with ^{111}In labeled cells, and abscess or inflammatory lesion was found to account for the scan findings. Eight of these patients had previously been studied [9]. An appendiceal abscess has been correctly diagnosed on ^{111}In leukocyte scan [31].

Although we only studied a small number of patients, our results strongly suggest that the test is not useful in the diagnosis of bacterial endocarditis or myocardial infarction. In experimental endocarditis in rabbits, labeled leukocytes were not diagnostic [32]; however, canine myocardial infarcts were visualized [33]. The difference in infarct detection is difficult to explain, but our negative findings were previously confirmed [34].

Uptake of ^{111}In white blood cells was noted in transplanted kidneys (three studies in two patients). The patients had progressive failure in renal function and clinical evidence of transplant rejection. Both kidneys showed histologic evidence of rejection. Renal uptake of labeled white blood cells could be due to infection, or rejection. If infection could be excluded by urine culture, rejection might be diagnosed by exclusion. Similar findings were recently described [35].

Our false-positive study is disturbing. In retrospect, the amount of uptake in the thigh lesion was less than we expect in abscesses, but at the time we interpreted it as a septic focus. It is conceivable that some lymphocytes or macrophages were labeled and they accumulated in the lymphomatous tumor.

Indium-111-labeled leukocytes provide an additional useful test for abscess detection. Whole body scintigraphy has the advantage that unsuspected or unusual septic foci have been detected (e.g., myocardial abscess [36] or intracranial mycotic aneurysm [37]). On rare occasions false-positive and false-negative results will be encountered. Therefore, we stress the importance of taking all clinical and laboratory evidence into the evaluation.

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