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In-111 Labeled Leukocyte Imaging: Analysis of Abdominal Uptake

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Indium-111標識白血球スキャン

（腹部異常集積の検討）

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膿瘍診断の目的で行われた Indium-111標識白血球スキャン140例について検討を加えた。患者134人の内58人は免疫能が低下しており、44人は臓器移植後であった。患者の81%は検査の際には何らかの抗生剤の投与を受けていた。

腹部に異常な集積が認められたのは52例でその60%は膿瘍あるいは感染症であった。33%は非感

染症病変への集積、7%は非炎症性病変への集積と判明した。

Indium標識白血球の集積の強さによってgradingを行ったが、膿瘍と他の病変を完全には区別できなかった。また、免疫力低下の有無は、抗生剤が投与されている条件下では検査の sensitivity, specificity に影響を与えなかった。

Introduction

Since its introduction by Thakur et al¹⁾²⁾, In-111 leukocyte imaging rapidly gained popularity due to its high sensitivity and specificity. Sensitivity of 71—100% and specificity of 72—97% have been reported in large series³⁾⁴⁾⁵⁾⁶⁾⁷⁾. This imaging is clinically used to detect “occult” abscess, however, it has been shown that this imaging is not specific for abscess⁸⁾⁹⁾. It has been anecdotally reported that these “non-abscess” lesions tend to accumulated less In-111 leukocytes than abscess, but little data have been available in the literature. Steroid administration is postulated to cause false negative studies, however, no study compared sensitivity of this test between the immunocompromised and the immunocompetent. We reviewed our experience to evaluate (1) whether or not sensitivity is impaired in immunocompromized patients; and (2) whether subjective grading of the intensity of abnormal In-111 leukocyte accumulation permits distinction between infectious and non-infectious lesions.

Material and Method

140 studies (134 patients) of In-111 leukocyte imaging performed at Presbyterian University Hospital of Pittsburgh to detect occult abdominal abscesses were retrospectively analyzed. The patients' age ranged 1 to 85 years old (average 40), including 68 males and 66 females. 58 cases were immunocompromized hosts,

including 44 transplant recipients (33 liver, 9 kidney, 2 heart), 7 patients with lymphoma/leukemia, 6 patients with steroid or other immunosuppressants, 1 case of immunodeficiency state of unknown etiology. 81% of the patients were on antibiotics at or within 2 days prior to re-injection of In-111 leukocytes.

(Preparation of In-111 leukocyte)

30—50 ml of venous blood was collected in 1000 units of preservation-free Heparin. The blood was allowed to sediment for 1 hour at a room temperature in a syringe with the needle tipped at a 30 degree angle up from the vertical. 3 ml of Hespan (6% Hetastarch in 0.95 Sodium Chloride) per 10 ml of blood was added to assist red blood cell (RBC) sedimentation. The supernatant was removed and centrifuged at 450 G for 6 min. per 20 ml plasma to produce a white blood cell (WBC) button, which was then resuspended in 5 ml of sterile normal saline for labelling. The overlying platelet-rich plasma was removed and re-centrifuged at 1500 G for 15 min. to obtain platelet free plasma and saved. 0.2 ml normal saline was added to In-111-oxine solution and 18.5—37 MBq (0.5—1 mCi) of In-111 oxine was then added dropwise to the WBC suspension and allowed to incubate for 30 min. at room temperature. During this period this was gently agitated 3 or 4 times. In order to separate the unbound from the bound label, the WBC suspension was centrifuged at 450 G for 6 min. to obtain the WBC button. The supernatant containing the unbound label was then removed. The WBC button and the supernatant was assayed for labeling efficiency. The cell button was gently resuspended in 8 ml of platelet free plasma. If the cell suspension was free of clumps, it was reinjected via a peripheral vein to the patient. An aliquot was obtained from the final preparation to determine cell viability by the Trypan Blue exclusion test. Depending on labeling efficiency (average 50—60%), 7.4 to 22 MBq (200 to 600 μ Ci) of In-111 leukocytes were re-injected intravenously.

ABO matched donor cells were used in 2 cases because of severe leukopenia (WBC<1000). The autologous leukocytes were used for the rest of the patients.

Anterior and posterior images of the thorax, abdomen and pelvis were routinely obtained at 20—24 hours using a gamma camera fitted with medium energy collimator with two 20% windows (172 and 247 KeV). Additional images of the head or extremities were added, when necessary. Data were collected for five minutes for each image. Informed written consent was obtained from all patients prior to the study.

When an abscess in the upper abdomen was suspected, Tc-99m sulfur colloid live-spleen scan was obtained within 2 days.

Abnormal studies in the abdomen were confirmed by autopsy, surgery, biopsy or laboratory studies except for 9 cases in which the cause for uptake was unknown. Negative studies were either confirmed by surgery or autopsy, or considered confirmed when reviews of the charts indicated no surgical intervention and the patients were either discharged or remained afebrile without antibiotics for a week. It is conceivable that some of the patients in whom an abscess or inflammatory lesion was not found had small lesions which responded to conservative treatment.

Results

72 studies of 140 In-111 leukocyte images were abnormal. Of these, 52 studies had abnormal uptake in the abdomen. 39 studies had abnormality in the thorax. 5 studies were associated with uptake outside the thorax or the abdomen.

The causes of abdominal uptake were then categorized into inflammatory and non-inflammatory processes. The inflammatory causes were further divided into infectious and non-infectious processes. The inflammatory process was defined as the local reaction of tissue to cell injury of chemical, physical and biologic causes. The infectious processes include cell injury due to biologic causes (bacterial, fungal and viral). The non-infectious causes included all inflammatory processes except infectious processes. The non-inflammatory process was defined as a disease or condition which does not primarily involve

Table 1 Analysis of abnormal accumulation in the abdomen

(43 studies, 45 sites)	
	No.
Inflammatory, Infectious	27
abscess	14
wound infection	3
enterocutaneous fistula	3
peritonitis	3
pseudomembranous colitis	1
diverticulitis	1
urinary tract infection	1
cytomegalovirus infection	1
Inflammatory, Non-infectious	14
pancreatitis	2
bile peritonitis	2
renal allograft rejection	2
open wound	2
acute tubular necrosis	2
radiation enteritis	1
bowel infarct	1
intussusception	1
catheter site	1
Non-inflammatory	4
GI bleeding	3
malignant tumor	1
	45

*Those cases with unknown etiologies were excluded.

Table 2 Comparison of sensitivity and specificity of In-111 leukocyte imaging between the immunocompromized and the immunocompetent

	No. of cases	
	immunocompromized	immunocompetent
TP	19	16
TN	32	31
FP	1	1
FN	0	2
	52	50
sensitivity	100%	89%
specificity	97%	97%

legend : TP=true positive, TN=true negative,
FP=false positive, FN=false negative.
All patients were on antibiotics.

Table 3 Grading of the Abdominal foci (35 sites)

	Grade				Total
	1	2	3	4	
Infections	2	8	6	3	19
abscess	1	5	2	3	
Non-infectious	5	7	—	—	12
Non-inflammatory	—	2	1	1	4
					35

*9 cases of liver transplant recipients were excluded.

inflammatory reaction and in practice included neoplasma and bleeding. The results were summarized in Table 1. Abnormal studies with unknown causes were excluded from the table.

To evaluate whether immunosuppression affect the sensitivity of In-111 leukocyte imaging for inflammatory processes, two groups of the patients (the immunocompromized <n=52> vs. the immunocompetent <n=50>) were compared in terms of sensitivity and specificity for abdominal inflammatory processes. All patients in these groups were on antibiotics at or within two days of the imaging. The results were summarized in Table 2. There was no statistical significance in sensitivity and specificity of two groups.

All abnormal foci in the abdomen except for those with liver transplant recipients and those in unknown etiologies were subjectively graded by intensity with reference to the liver, spleen or bone marrow and the results were summarized in Table 3 (Fig. 1-4). Grade 4 accumulation in non-inflammatory causes was that of a case with ovarian carcinoma in the pelvis with peritoneal dissemination (Fig. 4). Of 19 infectious sites, 9 were grade 3 or higher.

Discussion

Our results clearly demonstrated that In-111 leukocytes accumulate not only in abscesses but also in a variety of inflammatory or non-inflammatory processes. Although In-111 leukocyte uptake in the inflammatory processes is predictable if one considers the mechanism of inflammatory reaction to tissue injury, uptake in bleeding and neoplasm can not be explained simply by accumulation of granulocytes. The non-inflammatory causes of uptake may be accounted for labeling of contamination. By centrifugation,

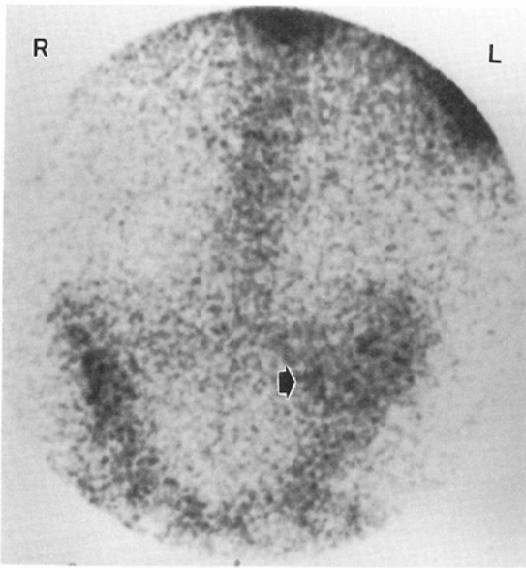


Fig. 1 Grade 1 accumulation in renal allograft rejection. 53 year old female with renal transplant 6 days prior to In-111 leukocyte study. Anterior image of the abdomen shows grade 1 uptake in the left iliac fossa (arrow), which corresponds to a poorly functioning renal allograft. Biopsy of the allograft revealed rejection. R: right, L: left.

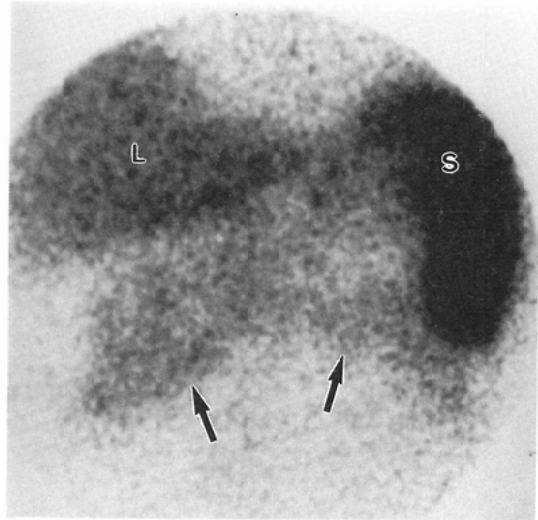


Fig. 2 Grade 2 accumulation in pancreatic abscess. 69 year old male with a history of cholecystectomy complicated by pancreatitis. Anterior image of the abdomen shows grade 2 uptake in the region of the pancreas (arrows). At laparotomy 1 week later, the abscess was drained, but the patient died of uncontrollable bleeding in the pancreatic bed 2 weeks later. L: liver, S: spleen.

which is now employed widely by nuclear pharmacy laboratories including our institution, it is almost impossible to obtain pure granulocytes without contamination. Dewnaje et al.¹⁰ found that only ($22\% \pm 14\%$) of total In-111 is bound to white cells (PMN and monocyte), ($25\% \pm 16\%$) to red cells, ($46\% \pm 20\%$) to platelets and ($7\% \pm 5\%$) bound to plasma in In-111 labeled white cell preparation with centrifugation and labeling with In-111 troplone. Doherty et al.¹¹ reported a contamination rate of 10%–20% with erythrocytes.

It is not surprising that GI bleeding results in false positive study, because of (1) relatively high rate of contamination by red cells in In-111 leukocyte preparation; (2) slow clearance rate of In-111 activity in the blood (As much as 4.6% of radioactivity remains in the blood at 22 hours after injection¹²).

The mechanism of false positive study in tumor is not fully understood. However, several hypotheses were proposed including (1) accumulation of free In-111 within the tumor probably due to inflammatory reaction to necrosis¹³, (2) increased blood pool in the tumor¹³, (3) accumulation of In-111 labeled lymphocytes¹⁴. Recently Fortner et al.¹⁵ postulated that tumor uptake of In-111 labeled leukocyte may be attributed to the presence of labeled monocytes and macrophages in tumor.

In our experience, GI bleeding and malignant tumor are particularly disturbing in image interpretation because they result in relatively intense accumulation (grade 3 and 4). Correlation with clinical information is important, however differentiation is sometimes impossible. Our patient with ovarian carcinoma underwent laparotomy because of strongly positive In-111 leukocyte study even though previous laparotomy revealed disseminated tumor in the pelvis and abdomen (Fig. 4).

Previous authors employed different criteria for positive test, including activity equal to or greater than the liver or spleen as positive test for or compatible with abscess^{5,16}; uptake equal to or greater than

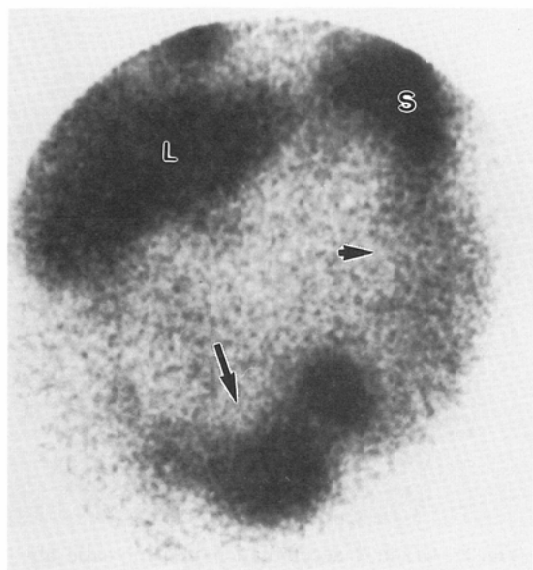


Fig. 3 Grade 3 accumulation in GI bleeding. 69 year old male with bleeding from the sigmoid colon confirmed by endoscopy. Anterior image of the abdomen and pelvis shows an uptake in the sigmoid colon (arrow). Note uptake in the descending colon due to regurgitant blood (arrow head). An uptake in the right hemithorax was considered to be due to ARDS. L: liver, S: spleen.

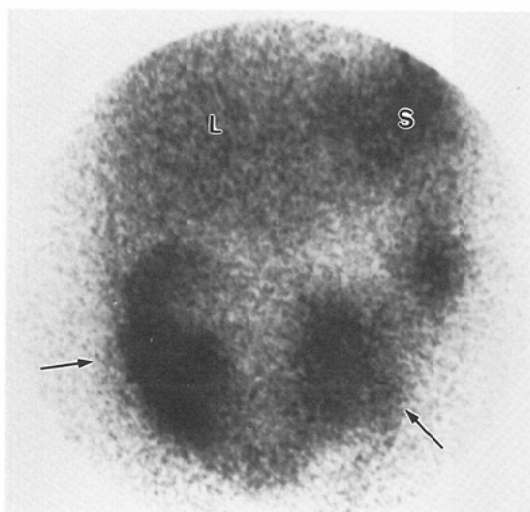


Fig. 4 Grade 4 accumulation in ovarian carcinoma (arrows). 65 year old female with 10 month history of lower abdominal pain and spiking fever. A laparotomy prior to the Indium-111 leukocyte scan revealed ovarian carcinoma with peritoneal seeding. The patient developed fever postoperatively, and another laparotomy was performed because of the intense accumulation in the pelvis. The patient was on chemotherapy at the time of imaging. L: liver, S: spleen.

liver as positive for infection¹⁷⁾; or all activity other than liver, spleen or bone marrow as significant¹⁸⁾. Some authors did not even provide any criteria for positive test⁶⁾⁷⁾¹⁴⁾. It is apparent, though, from our results that subjective grading does not allow distinction between abscess and other processes at least under the circumstances that antibiotics is administered to the patients. If Grade 3 or higher uptake had been considered positive, sensitivity of this test for abscess would have been 45% and 6 out of 11 abscesses would have been missed.

Our grading system of abnormal uptake is adopted from that of Gooding et al.⁴⁾. They studied 361 scans and found 12 abscesses, all of which were classified grade 4. Our results differed from Goodwin's in that only 3 of all our abscesses had grade 4 accumulation. All of our cases were on antibiotics and five of them were on immunosuppressants including steroids. Those five cases had uptake of grade 2, 3 and 4 respectively. Although it is not known whether their patients were on antibiotics or not, antibiotics administration in our patients may have decreased leukocyte accumulation.

Immunosuppression and antibiotics have been postulated to be one of the causes of false negative study¹⁹⁾. In our series, however, immunosuppression did not affect sensitivity of the test for abdominal inflammatory processes under the circumstance that antibiotics is administered to the patients. It is not yet clear whether immunosuppression alone affects the sensitivity of the test. A prospective study with a larger population would be necessary to clarify the role of immunosuppression and antibiotics in sensitivity of the test.

Conclusions

1. A variety of inflammatory and non-inflammatory conditions accumulate In-111 leukocytes.
2. Immunosuppression did not decrease sensitivity of the imaging for inflammatory processes under the circumstance that antibiotics is administered to the patients.
3. Subjective grading of intensity of abnormal In-111 leukocyte uptake did not permit the distinction between abscess and other conditions.

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