Scintigraphy with Indium-111-Labeled Homologous (Donor) Platelets in the Platelet Transfusion Refractory Bone Marrow Transplant Patient

Scott M. Hammersmith, Arnold F. Jacobson and David A. Mankoff
Division of Nuclear Medicine, Department of Radiology, University of Washington Medical Center; and Nuclear Medicine Section, Department of Veterans Affairs Medical Center, Seattle, Washington

Some bone marrow transplant patients who require multiple platelet transfusions as a consequence of post-transplant thrombocytopenia become refractory to these transfusions. As the spleen is the primary site of destruction for senescent and damaged platelets, splenectomy is a potential therapy for persistent thrombocytopenia. Scintigraphy with ^{111}In-labeled platelets has been used to identify increased splenic sequestration and destruction in various platelet disorders, especially idiopathic thrombocytopenic purpura, before consideration of therapeutic splenectomy, but this technique has not been widely described in platelet transfusion refractory bone marrow transplant patients. We report on the results of ^{111}In-labeled platelet scans in two such patients and review the pertinent literature in relation to the possible benefits and limitations of this scanning technique.

Key Words: bone marrow; indium-111; platelet transfusion therapy; splenectomy

J Nucl Med 1997; 38:1135–1138

Platelet transfusion therapy has made a significant contribution to clinical oncology practice, allowing for the administration of higher and potentially curative doses of chemotherapy. The availability of platelet transfusions has been of particular value to the successful application of bone marrow transplantation. However, 30%–70% of thrombocytopenic bone marrow transplant (BMT) patients develop platelet refractoriness, which prevents adequate improvement in platelet counts (PC) after transfusion (*1*). Risk factors for the development of refractoriness to platelet transfusions in BMT patients include nonimmune causes such as disseminated intravascular coagulation, amphotericin B toxicity, infection, splenomegaly, antibiotics, veno-occlusive disease and fever, and immune causes, primarily human leukocyte antigen (HLA) alloimmunization (*1*).

The term "platelet refractoriness" refers to a consistent inability to achieve a normal response to platelet transfusion, commonly determined from the corrected count increment (CCI) at 1 hr, defined as:

$$CCI = \frac{(\text{post-transfusion PC} - \text{pre-transfusion PC}) \times \text{body surface area (in meters squared)}}{\text{number of platelets in transfused} \times 10^{11}} \quad \text{Eq. 1}$$

where PC = platelet count in number of platelets/μl.

The lower limit of normal for CCI is 7500–10,000, with lower values considered to represent platelet refractoriness (*1*).

The primary goal in managing patients with platelet refractoriness is the prevention and treatment of bleeding complications. As splenomegaly and the associated increase in splenic sequestration and destruction of platelets is often a major cause of platelet refractoriness (*2*), splenectomy (surgical or embolic) is one means to improve response to platelet transfusions. Since all patients do not respond favorably to splenectomy, there has been considerable interest in the development of noninvasive methods to aid in selection of patients for surgery. One such method is scintigraphy with radiolabeled platelets.

Numerous investigators have used ^{111}In-labeled platelet scintigraphy to study the sites of platelet sequestration and destruction, and several different quantitative methods have been proposed (*4*). Generally, the sites of platelet sequestration are evaluated by determining the spleen-to-liver (S/L) ratios at one or more times, typically between 30 min (*4*) and 96 hr (*5*) postinjection.

Information on platelet scintigraphy in BMT patients is limited. Most studies using scintigraphy in platelet disorders have focused on patients with immune thrombocytopenic purpura (ITP). We present the results of two BMT patients with platelet refractoriness who underwent ^{111}In-platelet scintigraphy.

CASE REPORT

Patient 1

A previously healthy 42-yr-old man presenting for elective hernia repair was discovered to have chronic myelogenous leukemia in the chronic phase (Philadelphia chromosome positive) and subsequently underwent a BMT with fully HLA-matched marrow obtained from his sister. Engraftment occurred approximately 3 wk post-transplant. The immediate post-transplant course was complicated by mucositis, mild elevations of liver and renal function tests, brief atrial arrhythmias and a single episode of *Streptococcus viridans* septicemia treated with vancomycin. The patient was discharged from the BMT unit on Day 43 with no active infections and resolving oral graft versus host disease (GVHD) but was readmitted 4 days later with increasing mucositis and poor oral intake. This latter admission was notable for severe pancytopenia, markedly elevated liver function tests and Klebsiella septicemia. The patient was treated with granulocyte colony stimulating factor (GCSF) and required daily platelet transfusions. Although the patient's neutrophil count gradually improved, he remained dependent on platelet transfusions, with the platelet count rarely exceeding 20,000/μl (normal range 150,000–400,000/μl). One-hour CCIs ranged from 2727–4545. Transfusion with matched donor platelets failed to improve his response even though testing for antiplatelet antibodies against random donor platelets was negative. An ^{111}In-platelet study was performed on Day 83 to assess the extent of splenic sequestration of the donor platelets.

A 3-cc aliquot of a single donor platelet transfusion (six units; approximately 4×10^{10} platelets in the aliquot) was labeled with

Received Apr. 29, 1996; revision accepted Nov. 6, 1996.
For correspondence or reprints contact: Arnold F. Jacobson, MD, PhD, Nuclear Medicine Section (115), Department of Veterans Affairs Medical Center, 1660 South Columbian Way, Seattle, WA 98108.

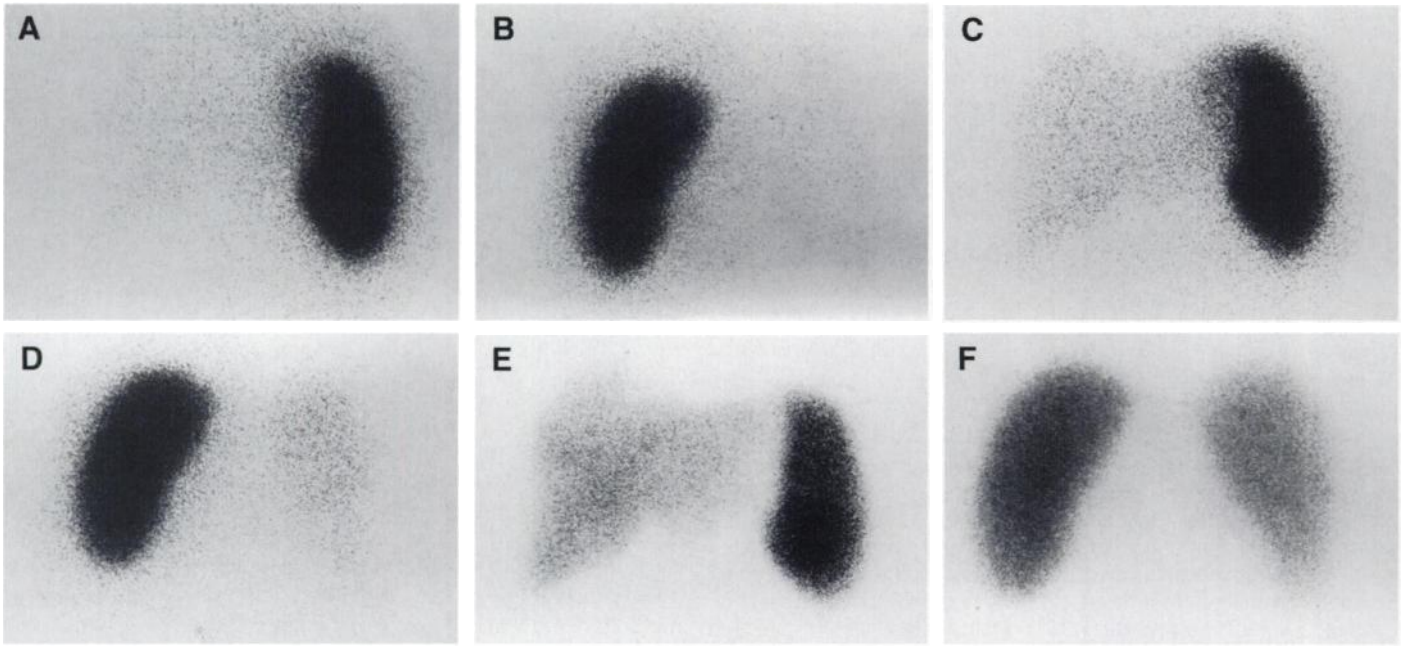

FIGURE 1. Patient 1. Liver and spleen images from ^{111}In-platelet scan at 2 (A,B) and 42 hr postinjection (C,D) and ^{99m}Tc-sulfur colloid scan (E,F). Virtually all labeled platelets are located in the spleen at the early imaging time, and even at 42 hr relative platelet activity in the spleen is significantly greater than on the colloid scan performed shortly thereafter.

36.7 MBq of ^{111}In-oxine (labeling efficiency of 94%) using the technique recommended by the International Committee for Standardization in Hematology (*6*). Anterior and posterior abdominal imaging with a large field of view gamma camera, medium-energy collimator and dual 20% windows was performed at 2, 18, 42 hr and at 6 days after injection. Images demonstrated increased uptake within a markedly enlarged spleen and initially only minimal uptake within a normal-size liver (Fig. 1). For each set of images, decay- and background-corrected geometric mean liver and spleen activity were determined from visually drawn regions of interest, and the S/L ratio was calculated (Table 1). In comparison with the normal control data of Stratton et al. (*5*), the S/L ratios were markedly elevated, with the total splenic activity remaining essentially unchanged while the liver activity gradually increased with time.

Subsequent to the 42 hr ^{111}In-platelet images, 244 MBq of ^{99m}Tc-sulfur colloid were injected, and anterior and posterior abdominal images were acquired 20 min later using the same camera and collimator but with a 20% energy window for ^{99m}Tc. The geometric mean S/L ratio was determined using the same method as for the platelet images. The ratio was 1.25, which was markedly increased from the values typically seen in BMT patients pretransplant (*7*), which is consistent with increased Kupffer cell activity within the spleen but considerably less than the platelet S/L ratio of 9.4. Estimated downscatter from the ^{111}In photons into the ^{99m}Tc window was $<10\%$.

Blood samples obtained at 0.5, 1, 4 and 5 hr and on Days 2–6 after injection were counted in a gamma well-counter. Platelet mean survival time was calculated by fitting a gamma variate function to the time-activity curve (*6*). The estimated platelet mean survival time was markedly decreased at 1.2 hr (normal range 6.4–9.9 days) (*8*), confirming accelerated destruction of the donor platelets.

TABLE 1
Results of the Indium-111-Labeled Platelet Study for Patient 1

Time	Liver counts*	Spleen counts*	S/L ratio
2 hr	10,465	204,659	19.6
18 hr	13,735	196,515	14.3
42 hr	21,080	198,936	9.4
6 days	34,807	208,682	6.0

*Geometric mean counts, decay- and background-corrected.

After the scintigraphic studies, a CT scan of the abdomen confirmed massive splenomegaly to 22 cm, and as the patient had received total-body irradiation as part of his BMT preparative regimen, further radiation to the spleen was not considered a safe option. Additionally, due to his multiple medical problems, surgery was considered too high-risk and clinical management was continued.

The patient's condition continued to deteriorate, and he died on Day 130 with fulminant liver failure and gram-negative sepsis. At autopsy, examination of the spleen showed congested red pulp, absent white pulp and multiple islands of extramedullary hematopoiesis.

Patient 2

A previously healthy 42-yr-old man being evaluated for left hip pain and a lytic lesion on pelvic radiographs was diagnosed with lymphoma, large-cell immunoblastic type, on a bone marrow biopsy. After a preparative regimen consisting of chemotherapy and total-body irradiation, the patient underwent peripheral blood stem-cell autologous bone marrow transplantation. Signs of engraftment were present on Day 18 with increasing white blood cell (WBC) and absolute neutrophil counts. He was discharged on Day 20 in stable condition with platelet counts of 30,000–40,000 and no active infection. However, the patient was readmitted on Day 56 with melena and severe thrombocytopenia (platelet count less than 20,000). His condition stabilized after platelet and RBC transfusions. Upper endoscopy failed to identify the cause for his gastrointestinal bleeding, and he was discharged 1 wk after admission. On Day 69, the patient was again admitted with recurrent melena and a hematocrit of 18. His platelet count persisted at less than 10,000 with 1-hr CCIs in the range of 2056–4522, despite one or two platelet transfusions daily. The patient's blood was negative for antiplatelet antibodies directed at HLA antigens, and HLA-matched donor platelets failed to provide significant improvement in the CCIs. A CT scan of the abdomen to

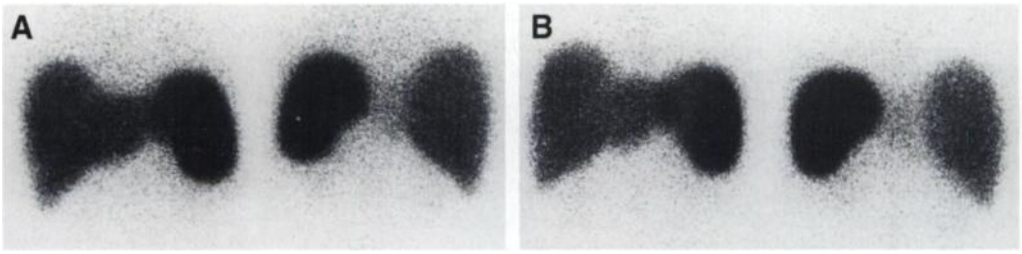

FIGURE 2. Patient 2. Liver and spleen images (anterior, left; posterior, right) from ^{111}In-platelet scan at 2 (A) and 48 hr postinjection (B). There is no significant change in relative uptake in the spleen between the early and late scans.

evaluate for possible intra-abdominal sepsis demonstrated mild splenomegaly.

An ^{111}In-platelet scan was performed on Day 76 using a 3-cc aliquot of single donor platelets (same composition as for Patient 1) labeled with 19.8 MBq of ^{111}In (labeling efficiency 90%). Abdominal imaging was performed at 15 and 35 min, and 2, 19, and 48 hr. Images demonstrated increased uptake in a mildly enlarged spleen and considerably more uptake in the liver than was observed in Patient 1 (Fig. 2). The S/L activity ratios were calculated as described for Patient 1, and the results are summarized in Table 2. While the early S/L ratios (15 min and 35 min) were moderately elevated, the ratios obtained at all later imaging times were within the normal range (1.6 ± 0.3) described by Stratton et al. (*5*). As in Patient 1, total spleen counts reached a plateau by 2 hr while total liver counts gradually increased with time.

Blood samples were obtained at 0.2, 0.7, 1.9, 2.6, 19.5 and 46 hr postinjection, counted and the results plotted to determine the platelet mean survival time. Because the data were a poor fit for a gamma variate, a bi-exponential curve was used, resulting in an estimated mean survival time of approximately 15 min. As in Patient 1, this confirmed markedly accelerated destruction of the labeled donor platelets.

Since the platelet scan showed moderate elevation of early S/L ratios, splenectomy was considered a reasonable approach to the patient's platelet refractoriness, and on Day 82 post-BMT, this surgery was performed. Pathological examination of the spleen showed mild enlargement to 15 cm and multiple foci of extramedullary hematopoiesis without evidence of recurrent lymphoma. Three days after the surgery, the CCI was significantly improved at 9866, and at 9 days after surgery, the CCI had further increased to 11,100. Subsequent results were as follows: at 18 days after splenectomy CCI = 29,712; at 34 days CCI = 40,363 and at 43 days CCI = 37,000. By Day 125 post-BMT (43 days post-splenectomy), requirements for platelet transfusion had decreased significantly to once every 3 days.

DISCUSSION

One of the major causes of platelet refractoriness in BMT patients is splenomegaly (*2*), which can result in rapid splenic sequestration and destruction of transfused platelets. Treatment with splenectomy is controversial, but one study showed that patients who underwent this procedure before bone marrow transplantation for chronic myelogenous leukemia required less platelet support and achieved better CCIs, and only 1 of 17 patients (6%) developed platelet transfusion refractoriness after BMT (*9*). However, in some patients, the liver and bone marrow are also major sites of sequestration and destruction of donor platelets, and in such patients splenectomy would likely be of limited effectiveness. An advantage of scintigraphy with radiolabeled platelets is that it allows examination of the spleen, liver and bone marrow with quantitation of the extent of splenic sequestration as a means to judge the potential utility of splenectomy. Use of ^{111}In-labeled platelet scans to identify the site of sequestration has been the most successful in patients with ITP (*3–5,11*).

TABLE 2
Results of the Indium-111 Platelet Study for Patient 2

Time	Liver counts*	Spleen counts*	S/L ratio
15 min	47,253	136,237	2.9
35 min	51,444	162,392	3.2
2 hr	83,952	149,940	1.8
19 hr	90,954	150,612	1.7
48 hr	96,767	161,871	1.7

*Geometric mean counts, decay- and background-corrected.

Three primary causes of thrombocytopenia are decreased platelet production, reduced platelet life span and enlargement of the splenic platelet pool (*10*). Kinetic studies using ^{111}In-labeled platelets have shown a good correlation between the degree of splenic platelet pooling and splenic platelet destruction, with the ratio of platelets destroyed (D) to those pooled (P) equaling approximately unity (*10*). This finding is independent of spleen size, mean platelet life span or the patient's underlying pathology (except in ITP where the D/P ratio varies from 0.5–2.0). With the exception of ITP patients, the splenic activity reaches equilibrium shortly after the injection of labeled platelets (by approximately 30 min) and remains essentially unchanged thereafter, also irrespective of mean platelet life span and spleen size (*10*).

Since one of the normal functions of the spleen is the removal of senescent or damaged platelets, it has been suggested that the identification of abnormal (or inappropriate) destruction requires demonstration of platelet destruction greater than splenic platelet pooling, which would be reflected by a continued rise in ^{111}In-platelet activity in the spleen after the time equilibrium is usually achieved (*10*). In our two patients, the decay-corrected counts in the spleen did not show a statistically significant increase with time after the establishment of equilibrium. Although this early achievement of equilibrium is normally seen in control subjects studied with autologous platelets, the percentage of activity appearing in the spleen compared to the liver was elevated in both our patients, indicating that the spleen was at least partially responsible for the increased destruction of donor platelets.

A comparison of our patients with those in the published literature is problematic due to the different threshold values for normalcy used by various authors. Heyns et al. (*13*) defined splenic sequestration as an S/L ratio of greater than 1.4, while Stratton et al. (*5*) used a value of greater than 1.9. Either threshold could be used for Patient 1, whose S/L ratio was markedly elevated at all times. For Patient 2, on the other hand, with a late S/L ratio of 1.7, the value used by Heyns et al. (*13*) would appear more appropriate. Perhaps more applicable to our patients is the description of three patterns of platelet kinetics (normal, rapid destruction and nonspecific) in individuals with chronic marrow hypoplasia and severe, refractory thrombocytopenia (*15*). The "normal" pattern was characterized by equilibration of platelets between circulating blood and the splenic pool accompanied by an early plateau of minimal liver activity,

while in the "rapid destruction" pattern, platelet life span was extremely short, resulting in a rapid early rise and a slow progressive later increase in splenic activity, as well as progressively increasing hepatic activity. In the "nonspecific" pattern, there were identical time-activity curves for the spleen and liver (both reaching a plateau early and then remaining unchanged over time) with a nearly equal distribution of counts between the spleen and liver. The results in our two patients appear to best correspond with the "rapid destruction" pattern, at least with regard to the time course of uptake in the liver.

CONCLUSION

Indium-111-platelet scanning may have a role in assessing the platelet transfusion refractory BMT patient for possible splenectomy, similar to its use in patients with ITP. While demonstration of in vivo platelet kinetics may assist in reaching a decision regarding splenectomy, consideration of the risks associated with persistent thrombocytopenia versus those of the surgical procedure itself will also be important. In addition, imaging protocols and threshold values specific for studies in BMT patients (using donor platelets) must still be defined before platelet scintigraphy can be routinely used as a standard examination for guiding therapeutic decisions.

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Indium-111-Leukocyte Imaging: A Case of Peritonitis Mimicking Inflammatory Bowel Disease

Lisa S. Gobar, Robin Graham and Katherine A. Harrison

Departments of Radiology and Surgery, Creighton University Medical Center, and Department of Radiology, University of Nebraska Medical Center, Omaha, Nebraska

Leukocytes labeled with ^{99m}Tc-HMPAO and ^{111}In have been used extensively in imaging inflammatory disorders, including inflammatory bowel disease (IBD), which has the appearance of tubular bowel activity. Peritonitis is inflammation of the serosal surfaces lining the peritoneal cavity which envelopes the bowel, giving a pattern of diffuse abdominal uptake on imaging. We present a case of an elderly man with surgically and pathologically confirmed peritonitis whose preoperative leukocyte scan mimicked the findings of IBD. Our findings suggest that diffuse peritonitis can mimic IBD on an ^{111}In-leukocyte scan.

Key Words: peritonitis; indium-111 leukocyte; inflammatory bowel disease

J Nucl Med 1997; 38:1138–1140

Peritonitis is an acute inflammation of the serosal surfaces lining the peritoneal cavity which also envelops the bowel. Involvement is usually diffuse, a finding that has been demonstrated on leukocyte scintigraphy (*1*). Clinicians investigating inflammatory and infectious disorders rely on leukocytes labeled with ^{99m}Tc-HMPAO and ^{111}In for diagnosis and treatment decisions. Common indications include evaluation of the fever of unknown origin, search for infection in known fluid collections and inflammatory bowel disease (IBD) (*1–4,6–11*). Abscesses are generally focal areas of leukocyte accumulation, and IBD is generally seen as tubular activity corresponding to segments of the small or large intestine. We present a case of pathologically confirmed peritonitis with the scintigraphic appearance of IBD.

CASE REPORT

A 73-yr-old man presented with malaise, weight loss, back pain and watery diarrhea for several weeks duration. The patient had a past medical history of steroid-dependent asthma, stroke, hypertension and arthritis. On presentation, he had mild abdominal tenderness, an elevated white blood cell count of 15.6 with 50% bands and metabolic acidosis. Iron deficiency anemia (hematocrit

Received Jun. 19, 1996; revision accepted Oct. 30, 1996.

For correspondence or reprints contact: Lisa Suzanne Gobar, MD, Department of Radiology, Creighton University School of Medicine, 601 N. 30th St., Omaha, NE 68131.