Bone-Marrow Imaging with Indium-111 Chloride in Aplastic Anemia and Myelofibrosis: Concise Communication

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Twenty-nine patients with aplastic anemia and 11 patients with myelofibrosis were evaluated with indium-111 chloride bone-marrow imaging, ferrokinetics, and bone-marrow core biopsies. There was good correlation between the erythrocyte cellularity of the marrow and the In-111 bone-marrow scan grades in most patients. In some, the overall scan grade tended to underestimate the erythroid elements because the core biopsy had been taken from the area of the greatest radionuclide concentration on the scan. In patients with aplastic anemia, there was good correlation between the plasma iron clearance $t_{1/2}$ and the scan grade. Less agreement was found in the comparison between the Fe-59 sacral and organ counts and the red-cell iron utilization. In patients with myelofibrosis, there was poor correlation between the surface counts over the sacrum and the red-cell iron utilization. Plasma iron clearances were abnormally short and were unrelated to the transferrin saturation levels. Eighteen patients were studied several times to evaluate their responses to steroid therapy. In all, there was good correlation between the bone-marrow imaging, the erythrocyte cellularity, ferrokinetics, and the patient's response to therapy. Indium-111 bone-marrow imaging is useful both in evaluating marrow erythroid activity and in following the response to therapy in patients with these diseases.

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Indium-111 chloride has been used recently to locate erythropoietic marrow, and several reports have shown its efficacy in such varied hematological conditions as aplastic anemia, myelofibrosis, red-cell aplasia, sickle cell anemia, leukemia, and lymphomas (*1–14*). If In-111 bone-marrow imaging proves to be an accurate method for assessing erythroid marrow, it could lessen the need for ferrokinetics and bone-marrow biopsies used to follow patients with certain hematologic diseases. We have compared In-111 bone-marrow imaging with simultaneous bone-marrow biopsies and ferrokinetic data in patients with aplastic anemia and myelofibrosis. Eighteen patients were studied in serial fashion to evaluate their response to steroid therapy (*15*).

METHODS AND MATERIALS

Forty patients were studied. Twenty-six had acquired aplastic anemia, one had Fanconi's anemia, and two had paroxysmal nocturnal hemoglobinuria with bone-marrow aplasia. Eight patients with aplastic anemia were under the age of 17. Eleven patients had myelofibrosis. All patients had severe depression of their red- and white-cell blood and platelet counts at the time of the imaging.

Bone-marrow imaging. Sixty-eight bone-marrow scans were performed on these 40 patients. In all cases, they were injected with carrier-free In-111 chloride in an acid pH without preincubation of the radionuclide with

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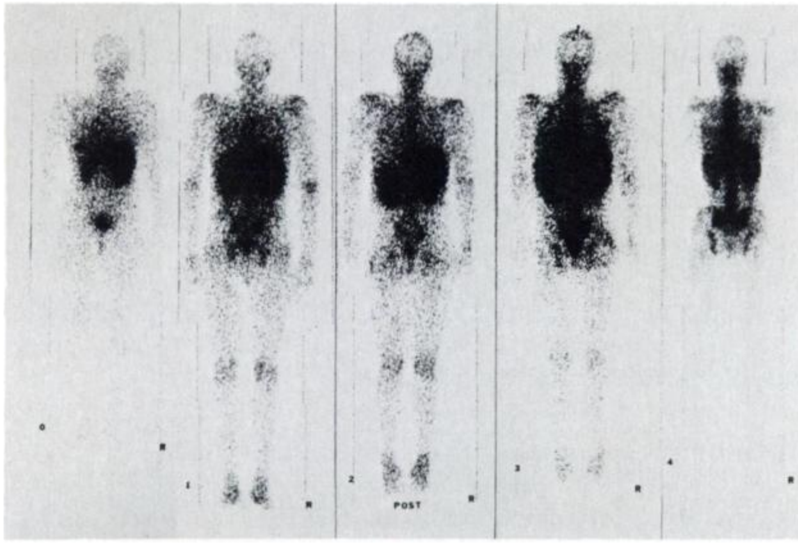

FIG. 1. Images graded on a five-point scale. Left to right: 0 was assigned when no activity was detectable in spine, sternum, or pelvis; 1 when activity was just above body background; 2 when there was increased activity without delineation of spine, sternum, or pelvis; 3 when there was higher activity, allowing better delineation of these areas; and 4 when there was sharp delineation of axial skeleton.

compatible plasma. Adults received 3 mCi, and for children the dose was reduced proportionately by body weight. Anterior and posterior rectilinear scans were obtained at 48 or 72 hr with a dual-probe rectilinear scanner giving 1:5 minification. All bone-marrow scans were subsequently interpreted independently by two observers without knowledge of the clinical status, biopsy results, or ferrokinetic data. Images were graded on a five-point scale (Fig. 1).

Four patients with aplastic anemia and one with myelofibrosis had Tc-99m sulfur colloid (Tc-99m SC) bone-marrow images two days before the In-111 injection. These were performed two hours after the injection of 10 mCi of Tc-99m SC. The dose was reduced proportionately for children.

Ferrokinetics. Sixty-one plasma iron clearances were performed, all within 3 wk of the imaging procedure. Each patient received from 5 to 20 μCi of carrier-free ferrous (Fe-59) citrate without preincubation with plasma. Samples were collected at 5, 15, 30, 60, 90, and 120 min after injection, and the $t_{1/2}$ of the plasma iron clearance was calculated.

Red-cell iron utilization was performed on 45 occasions. Utilization was calculated on the tenth day of sampling, using a previously determined red-cell mass. Forty-eight patients also had surface counting of various

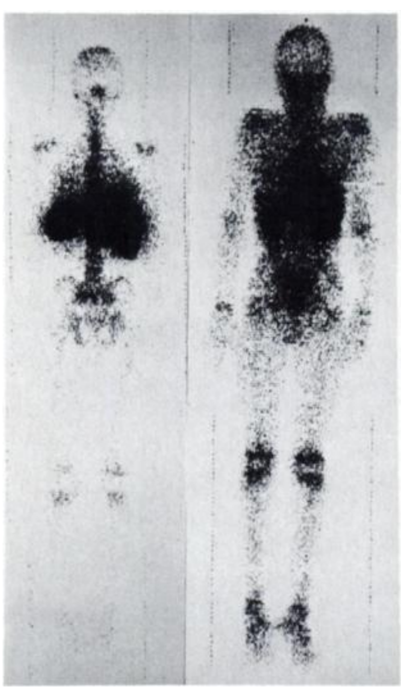

FIG. 2. Tc-99m SC scan on left and In-111 scan on right in a 14-yr-old patient showing greater uptake in axial skeleton with the colloid. Surface counting for Fe demonstrated no erythropoiesis in knees.

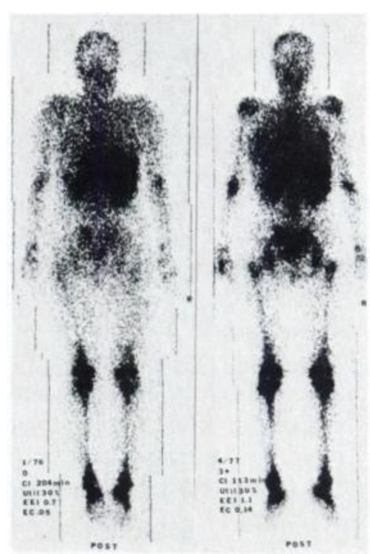

FIG. 3. Patient No. 1 (Table 2) with myelofibrosis, showing response to therapy. Peripheral activity represented erythropoietic bone marrow.

TABLE 1. BONE-MARROW IMAGES, BIOPSIES, AND FERROKINETICS BEFORE AND AFTER THERAPY IN PATIENTS WITH APLASTIC ANEMIA

Patient no.	Scan	EC	Clearance (min)	EEI	Util (%)	Response to therapy
1 9/27/77	1+	—	271	1.4	31	
1/9/78	4+	0.04	86	1.8	80	+
2 8/9/76	0	0.006	242	1.2	6	
1/23/78	2+	0.063	190	1.3	25	0
8/18/78	3+	0.13	75	1.6	55	+
3 2/25/76	0	—	273	1.4	29	
7/9/76	0	0.02	flat	—	—	0
9/9/78	2+	0.083	90	1.7	—	+
4 5/12/78	0	0.008	277	1.2	6	
9/18/78	2+	0.099	126	1.3	75	+
5 8/1/77	0	0.025	363	—	—	
12/1/77	1+	0.2	—	—	—	0
7/7/78	2+	0.13	122	—	—	+
6 1/8/76	0	0.1	180	1.3	59	
7/28/76	0	0.005	193	—	—	0
6/13/77	1+	0.01	137	1.5	49	0
8/30/78	1+	0.05	92	—	—	+
7 10/20/76	1+	0.025	185	1.1	69	
6/17/77	1+	0.005	—	—	—	0
1/17/78	1+	0.01	202	1.3	40	0
8/7/78	1+	0.008	133	1.5	41	0
1/17/79	2+	0.005	215	—	—	0
8 7/3/75	1+	0.01	128	1.3	80	
1/14/76	1+	0.03	—	—	—	+
9 9/6/77	1+	0.01	373	1.5	72	
1/9/78	1+	0.02	443	—	—	0
10 4/14/78	1+	0.03	247	1.3	5	
9/7/78	1+	0.01	239	—	—	0
11 8/29/77	0	0.05	725	—	—	
11/4/77	0	0.02	887	—	—	0
12 10/31/75	0	0.025	320	—	—	
10/20/76	0	0.005	307	1.1	<1	0

organs. External counting over the liver, spleen, heart, sacrum, and knee was done daily for a minimum of five days and in the majority for 10 days, using a single collimated sodium iodide detector. The effective erythrocyte index (EEI) was calculated by dividing the sacral counts on day 1 by the counts on day 5 (*16*).

Bone-marrow core biopsies. These were obtained from the anterior or posterior iliac crest on 62 occasions. All specimens were subsequently reviewed by two observers by visual inspection as unknowns. The erythrocyte cellularity (EC) of a bone-marrow biopsy was calculated from the marrow cellularity and the myeloid:erythroid ratio. For example, if the hematopoietic cellularity was 20% and the M:E ratio 3:1, the EC was calculated as (0.20) (0.25) = 0.050. The normal range was determined to be 0.048–0.12.

RESULTS

Aplastic anemia. Patients with marrow aplasia showed decreased indium concentration in their central skeleton in varying degrees that correlated with the severity of their illness. There was no evidence of compensatory marrow activity in the long bones of the adults studied. Six children (ages 3–13) demonstrated long-bone activity in the epiphyseal region, but only two (ages 3 and 10) showed evidence of erythropoiesis by external counting over the knee (Fig. 2). Two other children (ages 14 and 16) did not show increased activity in these areas, and external counting for iron showed no activity.

Analysis of the ferrokinetic data showed good correlation between the plasma iron clearance $t_{1/2}$ and the scan grade. Less agreement was found in the correlation of the EEI (sacrum) and the red-cell iron utilization with

TABLE 2. BONE-MARROW IMAGES, BIOPSIES, AND FERROKINETICS BEFORE AND AFTER THERAPY IN PATIENTS WITH MYELOFIBROSIS

Patient no.	Scan	EC	Clearance (min)	EEI	Util (%)	Response to therapy
1 1/12/76	0	0.05	204	0.7	27	
6/21/76	0	0.016	186	0.7	56	+
4/28/77	3+	0.12	113	1.1	27	+
1/12/78	2+	0.07	55	1.2	56	+
2 8/25/77	2+	0.14	42	1.3	73	
3/1/78	3+	0.1	—	—	—	+
3 8/9/76	0	0.025	426	1.2	2	
6/27/77	0	0.025	1736	0.9	<1	0
4 3/8/77	3+	0.045	24	—	—	
11/10/77	3+	0.045	—	—	—	0
5 10/29/75	3+	0.095	—	—	—	
9/29/78	2+	0.1	268	1.5	13	0
6 2/22/78	3+	0.008	38	1.8	35	
8/28/78	2+	0.025	37	1.7	71	+

the simultaneous indium image obtained. Comparison of the scan grade with the EC showed good correlation overall, but there was a tendency to underestimate "local" cellularity in several patients. When the cumulative data were analyzed, it was noted that in these latter patients the core biopsy had been obtained from the area of greatest tracer localization.

Reticuloendothelial bone-marrow images in four patients showed greater uptake in the axial skeleton with Tc-99m SC than with the indium (Fig. 2). In three there was activity in the long bones that was not demonstrated with indium. In the latter, the EEI (knee) revealed no evidence of erythropoiesis.

Myelofibrosis. Patients with myelofibrosis showed decreased indium concentration in the axial skeleton that correlated with the severity of the disease (Fig. 3). Nine showed tracer accumulation at the distal ends of the femurs and the proximal ends of the tibias. Surface counting (Fe-59) over the knees showed accumulation and release in four patients compatible with erythropoiesis. The iron clearance $t_{1/2}$ tended to be abnormally short in the majority of patients. This was unrelated to transferrin saturation values. There was poor correlation between the scan grade and the EEI (sacrum) and the red-cell iron utilization. There was good correlation between the scan grade and the EC, but in some patients the overall image tended to underestimate "local" cellularity for the same reason as noted above.

One patient with myelofibrosis was scanned with Tc-99m SC. In this patient the reticuloendothelial bone-marrow distribution was the same as that with indium. Surface counting over the knee in this patient demonstrated uptake and release of iron, indicating erythropoiesis.

Serial studies. Following therapy, 18 patients were studied again to evaluate their responses (Tables 1 and 2) (Fig. 3). In 16 patients, excellent correlation existed between the clinical response, bone-marrow images, bone-marrow biopsies, and ferrokinetics. One patient demonstrated improvement in her scan grade 3 mo before a clinical response was evident.

DISCUSSION

There is a definite clinical need for a noninvasive means of evaluating erythroid bone-marrow activity. In the past, colloid bone-marrow imaging has been used to evaluate the location of hematopoietic tissue but there may be a discrepancy between locations of reticuloendothelial marrow and hematopoietic elements in hematologic diseases (*17*). In four of our patients with aplastic anemia, in whom both agents were used, there was a discrepancy in two of the scans, with less indium concentration in the bone marrow than with the sulfur colloid.

Indium binds both in vitro and in vivo with transferrin, and after injection remains initially within the intravascular space (*18*). The plasma disappearance $t_{1/2}$ is approximately 10 hr (*19*). By 24 hr, radioactivity is demonstrated within the normal skeleton in what corresponds to the expected bone-marrow distribution. The exact location of the indium within the bone marrow is controversial. In the rat model it has been shown to be an effective marker for early phases of marrow iron uptake (*20*). In contrast, when rabbit bone marrow is irradiated, iron uptake is depressed but there is no change in either the indium or the Tc-99m SC uptake (*21*). In three patients with a "preleukemic" state associated with red-cell aplasia, there was good correlation between the colloid and the indium scan but no uptake was detected with Fe-52 (*7*). In four other patients with red-cell aplasia, however, good correlation was seen between the indium image and the presence of erythroid marrow (*3,7,11*).

Our study suggests that in patients with aplastic anemia and myelofibrosis the indium is distributed within the skeleton in the same distribution as the erythroid marrow except in the extremities of children. In six children with aplastic anemia there was indium concentration in the epiphyseal regions of the lower extremities, but only two showed evidence of erythropoiesis by external counting over the knee. With this exception, there was good correlation between the marrow erythrocyte cellularity (EC) and the In-111 bone-marrow imaging in patients with all degrees of severity of disease. As have others, we have found the scan to be quite useful in selecting the bone-marrow sites for biopsies (*8,10*). Furthermore, it lends itself well to follow-up of the patient's response to therapy, thereby possibly diminishing the need for bone-marrow core biopsies and repeated ferrokinetic studies. In addition, an improvement in the scan may herald the clinical response to therapy before it is perceived by other tests.

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