CASE REPORT

The Radioindium Bone-Marrow Image in Acute (Malignant) Myelofibrosis

Michael C. Perry and Richard A. Holmes

University of Missouri-Columbia and the Harry S. Truman Memorial Veterans Hospital, Columbia, Missouri

A patient with a rapidly fatal case of acute myelofibrosis had a radioindium bone-marrow image that unexpectedly showed a normal pattern of distribution, unlike the more typical forms of chronic myelofibrosis or agnogenic myeloid metaplasia. The rapid progression of the disease and the unique handling of radioindium by the reticuloendothelial system may explain the discordant findings.

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In 1963 Lewis and Szur described five patients with an acute form of agnogenic myeloid metaplasia (AMM) characterized by pancytopenia, myeloblasts in the peripheral blood, and diffuse marrow fibrosis (*1*). Because these patients lacked splenomegaly and had a rapidly fatal course without autopsy evidence of acute leukemia, this entity was called "acute myelofibrosis." Since its original description, 20 cases have been reported under a variety of titles (*2–6*). We recently studied a case of acute myelofibrosis (AMF) in which the radioindium bone-marrow image showed an unexpected pattern of distribution. This report discusses these findings and the possible reason(s) for its occurrence.

CASE HISTORY

A 71-year-old white male was transferred to our institution from another hospital with the diagnosis of "megakaryocytic leukemia." For 18 mo before his admission he had experienced increasing fatigue and malaise, with progressive dyspnea for the last 12 mo. On admission he was a weak, pale, elderly male who appeared acutely and chronically ill. Petechial lesions were present in the oropharynx, and dried blood appeared in the nares. Neither lymphadenopathy nor hepatosplenomegaly was demonstrable.

Laboratory results revealed a hemoglobin of 5.6 g/dl and a white-cell count of 33,000/mm^3; the differential gave 35% segmented neutrophils, 11% bands, 4% metamyelocytes, 8% myelocytes, 3% promyelocytes, 26% myeloblasts, 10% lymphocytes, and 3% monocytes. Nineteen nucleated red cells per 100 WBC were seen on the peripheral blood smear, along with normochromic-normocytic red cells, moderate anisopoikilocytosis, and rare tear-drop-shaped red cells. The platelet count was 33,000/mm^3, and an occasional giant platelet was seen.

The BUN was 58 mg%, creatinine 1.9 mg%, SGOT 143 IU, SGPT 66 IU, alkaline phosphatase 113 IU, uric acid 11.8 mg%, LDH >2400 IU, and CPK 117 IU. The screen to detect disseminated intravascular coagulation was negative. The leukocyte alkaline phosphatase score was 273 (normal 10 to 100) and a Coombs test was negative. Subjective minimal splenomegaly was the only abnormality detected on a radiocolloid liver/spleen image. An indium-111 chloride ($^{111}InCl_3$) bone-marrow image revealed intense uptake in the liver and spleen but a normal pattern of marrow distribution throughout the axial skeleton (Fig. 1B).

Attempts at bone-marrow aspiration were unsuccessful, but a marrow biopsy with the Jamshidi needle produced a satisfactory specimen. It revealed a predominance of loose fibroblasts and large numbers of megakaryocytes in a stroma of fibrosis but without evidence of hematopoietic marrow. No stainable iron, tumor cells, or granulomata were demonstrable.

During his 4-wk hospitalization treatment consisted of red cell and platelet transfusions, prednisone, and halotestin. Less than a month after his discharge he died quietly at home, and no autopsy was performed.

DISCUSSION

To date, 21 cases of acute myelofibrosis have been reported from ten medical centers (*1–6*). Most of the patients were elderly males with an average age of 55 yr (range 16–84 yr) and a male-to-female ratio of 7 to 3. The presenting symptoms reflected the underlying pancytopenia, with complaints of lethargy, fatigue, weakness, bleeding, and fever. Except for pallor, physical examination has been surprisingly benign, with the absence of splenomegaly or lymphadenopathy. Less than a third of the patients (6 of 21) showed moderate degrees of hepatomegaly.

Each patient was severely anemic, with an average of hemoglobin of less than 7 g/dl. Tear-drop poikilocytes were rare. Three quarters of the patients (16 of 21) were leukopenic, and half (11 of 21) had white-cell counts of greater than 1500/mm^3. Twenty of 21 had thrombocytopenia ranging from 5000–372,000/mm^3 (average 58,000/mm^3), and all were plagued by bleeding episodes. Each patient demonstrated myeloblasts in the peripheral blood

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For reprints contact: Richard A. Holmes, Nuclear Medicine Service, Harry S. Truman Memorial Veterans Hospital, 800 Stadium Road, Columbia, MO 65201.

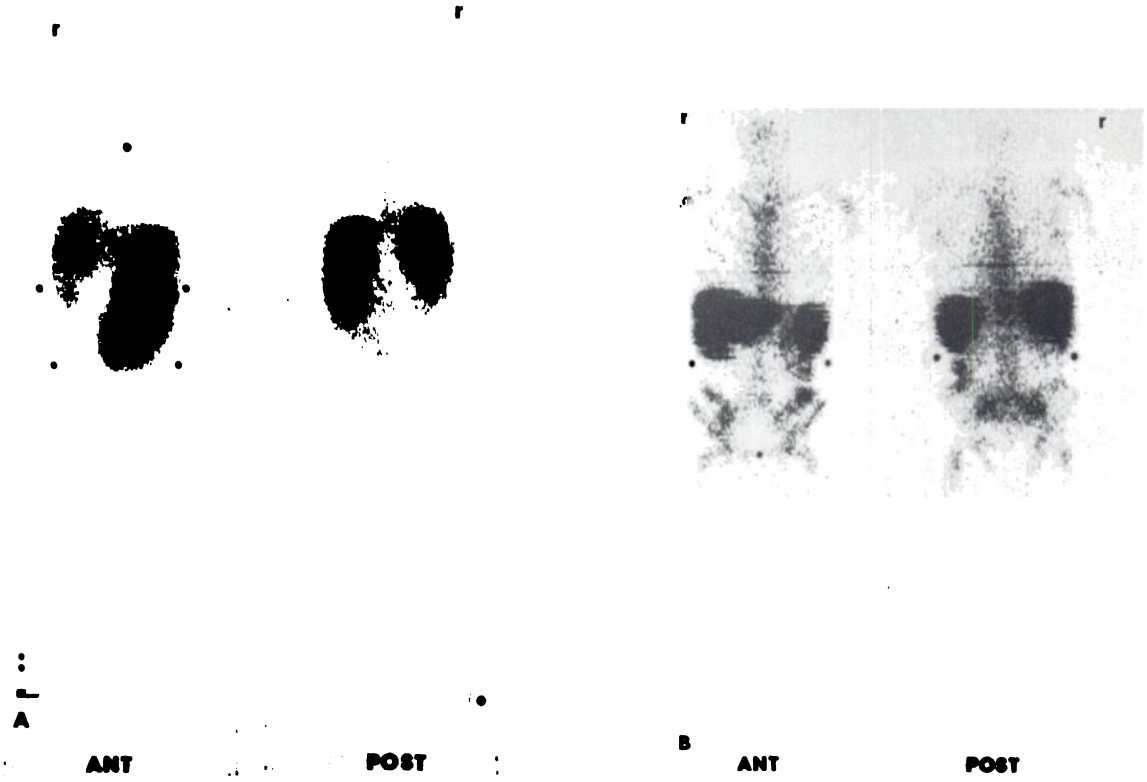

FIG. 1. (A) Patient with classical advanced myelofibrosis. In-111-chloride bone-marrow image shows absence of skeletal marrow activity but massive splenomegaly and hepatomegaly with prominent radioindium uptake, probably indicating extramedullary hematopoiesis. (B) Patient with acute malignant myelofibrosis (AMM) demonstrating nearly normal skeletal marrow distribution and intense uptake in liver and spleen on radioindium marrow image. (Intense focus, left pelvic rim, is recent biopsy site.)

(range 1-100%) that related to the stage of the disease. Sixteen of the 21 showed immature normoblasts in the peripheral-blood smear, producing a leukoerythroblastic blood picture.

Conventional bone-marrow aspiration characteristically results in a "dry tap." The marrow biopsy consistently demonstrates megakaryocytic hyperplasia and dense collagen or reticulin fibrosis obliterating the marrow space; increased numbers of myeloblasts are conspicuously absent. Autopsy material has confirmed the marrow biopsies and frequently demonstrates hematopoiesis in the liver and spleen.

The AMF patient usually survives less than 6 mo (range 1–15 mo) regardless of the therapy. While no uniform method of therapy has been tried, most patients are treated symptomatically with blood-component transfusions and corticosteroids. In the few instances where cytotoxic therapy was tried, it was ineffective.

The intriguing feature of this case is the nearly normal pattern of distribution of the $^{111}In\ Cl_3$ bone-marrow image. The pathognomonic image pattern of patients with agnogenic myeloid metaplasia shows absence of axial and appendicular bone marrow activity, and exclusive uptake of the radiotracer by the massively enlarged spleen and liver (Fig. 1A). In contrast, the image pattern in our patient clearly delineates the axial-skeleton marrow with moderate extension of the In-111 activity into the proximal long bones of the extremities (Fig. 1B). Apparently increased radiotracer concentration can also be seen in the normal-sized liver and enlarged spleen.

Although it is plausible to attribute the discordant radioindium distribution pattern in our patient to the acute and rapidly progressive nature of the disease, the discordance could relate to the biokinetics of injected indium. When administered intravenously, ionic radioindium is rapidly and avidly bound by the beta globulin transferrin, and clears slowly ($T_{1/2}$ = 6–10 hr) from the circulation (7). Like iron, the radioindium is transported to and deposited in the bone marrow at sites of active erythropoiesis (*8*). Unlike iron, however, less than 4% of the radioindium is detectable in circulating erythrocytes at 8–10 days (*9*). This may be due to pronounced radioindium elution from the red cell, but to date no data have emerged to confirm that the erythron incorporates indium. Rather, evidence has accrued that the In-111-transferrin complex is primarily phagocytized by marrow histiocytes (iron-storage cells) and becomes a permanent and relatively inactive member of the iron pool beyond the first 24 hr. This would explain the normal radioindium bone-marrow distribution in our patient in face of the depleted marrow iron stores.

The apparently increased concentration of radioindium in the liver and spleen of our patient suggests the development of extramedullary hematopoiesis. Enhanced uptake of radioindium due to increased blood flow to extramedullary marrow is a viable consideration for this observation (*8*).

AMF shares several features with classical AMM. Both demonstrate leukoerythroblastic peripheral-blood pictures, pancytopenia, and bone-marrow fibrosis. In its exceedingly short survival and the absence of massive splenomegaly, AMF differs dramatically from AMM, where the average patient survives 5 yr or more. The rapidly fatal course of AMF mimics that of acute myeloblastic leukemia (AML), with both showing, depending on the stage of the disease, overwhelming numbers of circulating myeloblasts. In a recent attempt to establish a clinical histologic relationship between AMF and AML, Bird and Proctor (*10*) reviewed the marrow biopsies of four patients displaying such an illness to determine the degree and clinical significance of the fibrosis. They concluded that the two diseases were histologically indistin-

guishable and represented acute leukemia with myelofibrosis. The radioindium bone-marrow image in our patient supports this conclusion because the pattern of distribution is identical to that found in acute leukemia.

REFERENCES

1. LEWIS SM, SZUR L: Malignant myelosclerosis, *Br Med J* 1: 472-477, 1963
2. WOOD EE, ANDREWS CT: Subacute myelosclerosis. Report of three cases. *Lancet* 2:739-743, 1949
3. MITUS WJ, COLEMAN N, KIOSSOGLOU JA: Abnormal (Marker) chromosomes in two patients with acute myelofibrosis. *Arch Intern Med* 123:192-197, 1969
4. BERGSMAN KL, VAN SLYCK EJ: Acute myelofibrosis. An accelerated variant of agrogenic myeloid metaplasia. *Ann Intern Med* 74:232-235, 1971
5. LUBIN J, ROZEN S, RYWLIN AM: Malignant myelosclerosis. *Arch Intern Med* 136:141-145, 1976
6. FABICH DR, RAICH PC: Acute myelofibrosis. A report of three cases. *Am J Clin Pathol* 67:334-338, 1977
7. HOSAIN F, MCINTYRE PA, POULOSE F, et al: Binding of trace amounts of ionic indium-113m to plasma transferrin. *Clin Chim Acta* 24:69-75, 1969
8. STAUB RT, GASTON E: ^{111}In-chloride distribution and kinetics in hematologic disease. *J Nucl Med* 14:456-457, 1973
9. FARRER PA, SAHA GB, KATZ M: Further observations on the use of ^{111}In-transferrin for the visualization of bone marrow in man. *J Nucl Med* 14:394-395, 1973
10. BIRD T, PROCTOR J: Malignant myelosclerosis. Myeloproliferative disorder of leukemia? *Am J Clin Pathol* 67:512-520, 1977