Bone Marrow Regeneration After Hormonal Therapy in Patients with Bone Metastases from Prostate Carcinoma

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Two patients with prostate carcinoma and bone metastases were treated with hormonal therapy. Radioimmune imaging of bone marrow performed with ^{99m}Tc-labeled antigranulocyte antibody BW 250/183 before treatment demonstrated absence of granulopoietic bone marrow in extensive regions of the central and proximal peripheral skeleton, indicating diffuse bone marrow invasion. Bone marrow scans performed after treatment demonstrated presence of granulopoietic bone marrow in these regions, indicating bone marrow regeneration. This finding was consistent with favorable response to treatment.

J Nucl Med 1991; 32:2295–2298

The most common form of metastatic spread from prostate cancer is to the bone, which occurs in about 85% of patients dying of prostate cancer (*1*). It has been shown that bone scans are highly sensitive tests for detecting skeletal involvement in patients with prostate cancer (*2–5*). Conventional bone scans demonstrate bone metastases in approximately 23% of all patients judged free of disease by a routine bone survey (6). Soloway et al. (*7*) stratified patients with metastatic prostate cancer depending on the extent of the disease seen on initial bone scans. Their grading system correlated with survival. It has been shown that patients determined to have progression on bone scans at 6 mo have a survival of 41% versus 88% for those who have improvement or stability on the scan (*8*). Therefore, serial bone scans provide significant prognostic information. However, assessment of response to treatment in prostate cancer remains a problem. Interpretation of bone scans shortly after treatment may be difficult mainly due to the flare phenomenon (*9*). Assessment of improvement in patients with widespread metastatic bone disease is hampered by the difficulty in counting, sizing, and comparing activity in a large number of skeletal lesions. Stability of the bone scan shortly after treatment may not indicate absence of response (*8*).

Received Feb. 14, 1991; revision accepted Jun. 26, 1991.

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In breast cancer and malignant lymphoma, radioimmunoimaging of bone marrow can demonstrate bone marrow invasion before bone tissue invasion is apparent on conventional bone scans (*10,11*). To assess bone marrow involvement and its response to hormonal therapy in patients with prostate carcinoma, a prospective study is being conducted in our institution using ^{99m}Tc-antigranulocyte monoclonal antibody BW 250/183 (AGMAb) (Behringwerke, Marburg, FRG) to perform bone marrow scans. We report two patients in whom bone marrow scans showed bone marrow regeneration shortly after treatment.

CASE REPORTS

Patient 1

A 61-yr-old, male presenting with prostate carcinoma diagnosed by transrectal needle biopsy, histologic type Gleason 5/5, was studied for initial staging. At that time, the patient presented with generalized bone pain and with a weight loss of 8 kg in 3 mo. A conventional bone scan performed after intravenous administration of 20 mCi of ^{99m}Tc-methylene diphosphonate showed widespread metastatic involvement of the entire axial and proximal appendicular skeleton. The ^{99m}Tc-AGMAb bone marrow scan, performed 5–6 hr after intravenous injection of 0.5 mg of antibody labeled with 20 mCi of ^{99m}Tc (*11*), showed marked absence of granulopoietic bone marrow in the central and proximal peripheral skeleton indicating bone marrow tumoral invasion (Fig. 1A). X-ray examinations showed skeletal blastic lesions. Laboratory test findings were: leukocyte count of 4,700 per mm^3, hemoglobin of 11.2 g/dl, platelet count of 225,000 per mm^3, erythrocyte sedimentation rate of 121 mm/hr, alkaline phosphatase of 754 U/liter (nr 98–279), total acid phosphatase of 208 U/liter (nr 0–6.9), and prostatic acid phosphatase of 190 U/liter (nr 0–2). The patient was treated with 3.6 mg/28 days of goserelin (Zoladex®, ICI Farma) (a luteinizing hormone-releasing hormone agonist that reduces testosterone to castrate levels) and 250 mg/8 hr of flutamide (a nonsteroidal anti-androgen). Three months later, laboratory tests showed an increase in alkaline phosphatase (1547 U/liter) and a decrease in total acid (18.1 U/liter) and prostate acid (5.7 U/liter) phosphatases.

Six months after starting treatment, the patient was restudied. He presented relief of bone pain and gain in weight. The bone scan performed at that time did not show any differences from the initial study. The bone marrow scan demonstrated defects in the bone marrow, but presence of granulopoietic bone marrow in extensive regions of the central and proximal peripheral skel-

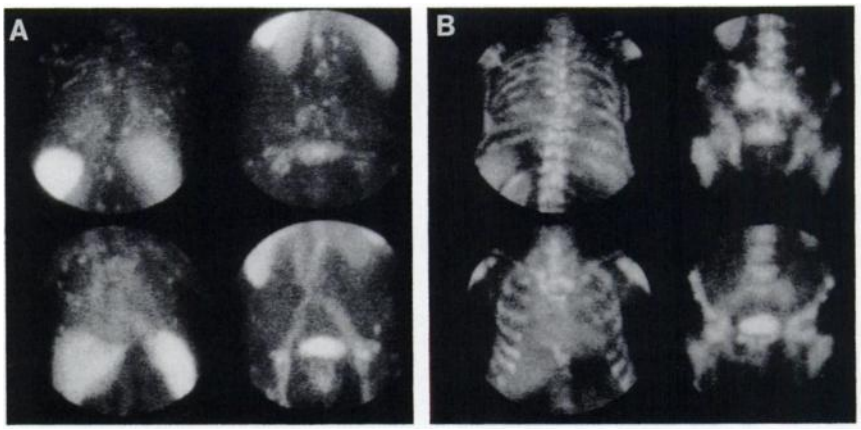

FIGURE 1. (A) Case 1: Bone marrow scan performed before treatment showing absence of bone marrow in extensive regions of the central and proximal peripheral skeleton due to bone marrow invasion. (B) Case 1: Bone marrow scan performed after treatment showing bone marrow defects and presence of bone marrow in extensive regions of the central and proximal peripheral skeleton, indicating bone marrow regeneration.

eton (Fig. 1B). X-ray examinations showed persistent skeletal blastic lesions. Laboratory tests showed leukocyte count of 3,900 per mm^3, hemoglobin of 12.6 g/dl, platelet count of 270,000 mm^3, erythrocyte sedimentation rate of 7 mm/hr, alkaline phosphatase of 670 U/liter, total acid phosphatase of 18.3 U/liter, and prostatic acid phosphatase of 4.6 U/liter.

Patient 2

A 82-yr-old male, presenting with prostate carcinoma diagnosed by transrectal biopsy, histologic type Gleason 5/5, was studied for initial staging. The patient presented with asthenia, anorexia, weight loss, and bone pain. The bone scan was interpreted as corresponding to diffuse metastatic disease. The bone marrow scan showed absence of granulopoietic bone marrow in the central and most of the proximal peripheral skeleton indicating extensive bone marrow invasion (Fig. 2A). X-ray examinations showed osteolytic and osteoblastic lesions in the central skeleton. Laboratory test findings were: leukocyte count of 4,400 per mm^3, hemoglobin of 8.6 g/dl, platelet count of 78,000 per mm^3, erythrocyte sedimentation rate of 100 mm/hr, alkaline phosphatase of 282 U/liter, total acid phosphatase of 5.9 U/liter, and prostatic acid phosphatase of 2.3 U/liter. The patient started treatment with goserelin and flutamide. Laboratory tests performed 3 mo later showed an increase in alkaline phosphatase (567 U/liter), an increase in total acid phosphatase (9.4 U/liter), and a decrease in prostatic acid phosphatase (0.9 U/liter).

Six months after starting treatment, the patient was restudied. There was improvement in his clinical status in that there was palliation of bone pain and he had gained weight. The bone scan did not differ from the initial study. The bone marrow scan demonstrated presence of granulopoietic bone marrow in the central and proximal peripheral skeleton (Fig. 2B). X-ray examinations showed no changes. Laboratory tests showed a leukocyte count of 5,700 per mm^3, hemoglobin of 11.5 g/dl, platelet count of 153,000 per mm^3, erythrocyte sedimentation rate of 22 mm/hr, alkaline phosphatase of 266 U/liter, total acid phosphatase of 8.4 U/liter, and prostatic acid phosphatase of 0.9 U/liter.

DISCUSSION

Retrograde blood flow through the paravertebral venous system communicating with the sinusoids of the bone marrow and the enhanced susceptibility of bone marrow, because of the special microanatomical aspects of its vasculature, determine the seeding of tumor cells in bone marrow (*12*). This would be followed by invasion of bone tissue matrix and finally by invasion of the cortical bone.

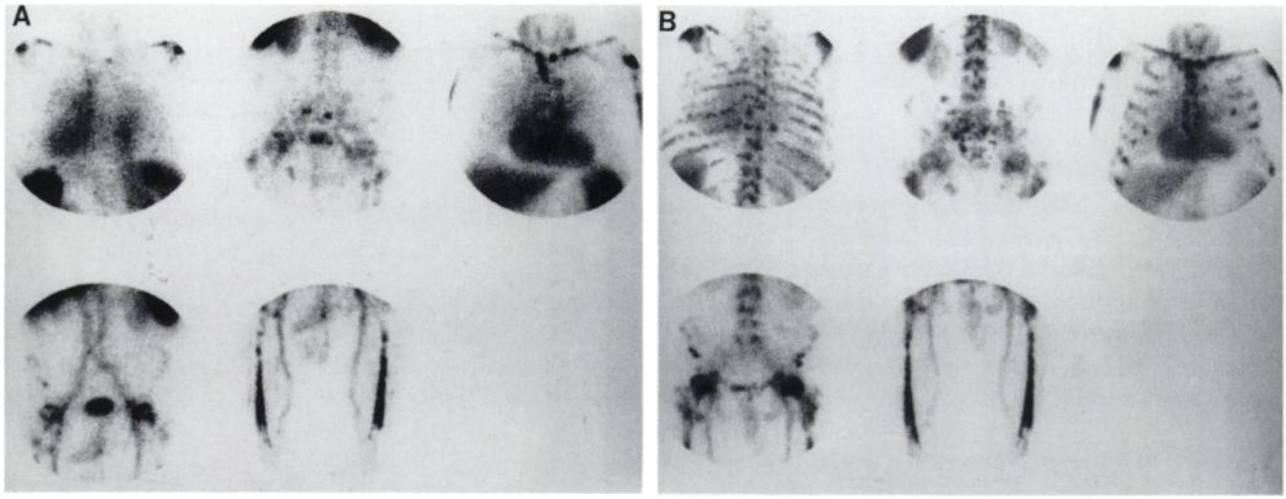

FIGURE 2. (A) Case 2: Bone marrow scan performed before treatment showing absence of bone marrow in most of the central and proximal skeleton due to bone marrow invasion. (B) Case 2: Bone marrow scan performed after treatment showing bone marrow defects and presence of bone marrow in extensive regions of the central and proximal peripheral skeleton, indicating bone marrow regeneration.

Ito et al. (*13*) suggested that colloid bone marrow scintigraphy could provide proof of metastatic spread in cancer patients at an earlier stage than conventional bone imaging. However, colloid bone marrow scans were hampered by liver and spleen accumulation and the technique did not gain general acceptance. Haddock et al. (*14*) performed bone marrow scintigraphy with ^{99m}Tc-nanocolloid in patients presenting with prostate carcinoma. They concluded that bone scans were more sensitive than bone marrow scans, but that bone marrow scans could identify patients at risk from fatal marrow suppression following systemic chemotherapy and total-body irradiation. Recently, Reske et al. (*15*) studied 25 patients with prostate carcinoma and reported that immunoscintigraphy of granulopoietic bone marrow performed with ^{99m}Tc-AGMAb was more sensitive than bone scans in detecting metastatic bone involvement.

We report two cases in which ^{99m}Tc-AGMAb bone marrow scans performed at initial staging showed absence of granulopoietic bone marrow in extensive regions of the central and proximal peripheral skeleton (Figs. 1A and 2A), indicating extensive metastatic bone marrow invasion. These findings correlated with laboratory tests since both patients presented with anemia and increases in alkaline and prostatic acid phosphatases. Three months after hormonal therapy, both patients presented with a peak of alkaline phosphatase with a decrease in prostatic acid phosphatase. This is related to the process of recalcification in prostate cancer patients with bone metastases and response to treatment. Six months after treatment hemoglobin levels increased, alkaline phosphatase decreased, and prostatic acid phosphatase normalized in one patient and decreased in the other. In both patients, ^{99m}Tc-AGMAb bone marrow scans showed presence of bone marrow in regions of the central and the proximal peripheral skeleton where it was previously absent (Figs. 1B and 2B). This finding indicated granulopoietic bone marrow regeneration, correlated with laboratory tests, and indicated good response to the hormonal therapy. Bone scans at that time were stable compared to those performed at initial staging.

Bone marrow regeneration has been studied in experimental animal models (*16–17*) and in patients with oncologic and hematologic diseases (*18–20*). In serial iliac-crest bone marrow biopsies, bone marrow regeneration is observed as an increase in the number of clusters of hematopoietic progenitors in the studied specimens (*18*). Bone invasion from hematologic neoplasms and solid tumors suppress normal hematopoiesis resulting in neutropenia, anemia, and thrombocytopenia. The most effective way of increasing hematologic cell production is to clear the malignancy from the marrow with chemotherapy (*21*). When malignant cells have been cleared from bone marrow space, regenerated hematopoietic tissue may grow in the bone marrow cavity.

Indium-111-chloride bone marrow scanning has been used to evaluate erythropoietic bone marrow response to steroid therapy in aplastic anemia and myelofibrosis (*22*). Sayle et al. (*22*) studied eighteen patients with ^{111}In bone marrow scans several times and, after grading the scans on a five-point scale, found correlation between bone marrow images and clinical response. The major drawback of ^{111}In chloride bone marrow images is the poor delineation of the central skeleton. Since the central skeleton is the primary site of bone metastases from extraosseous malignancies, assessment of central bone marrow is necessary in the evaluation of patients with metastatic bone marrow invasion. Technetium-99m-AGMAb bone marrow scans provide excellent delineation of central and proximal peripheral bone marrow, allowing precise detection of bone marrow invasion and visualization of bone marrow expansion (*11*).

Our report provides evidence of granulopoietic bone marrow regeneration by a noninvasive radioimmune imaging method. A noninvasive method to demonstrate and visualize the sites of bone marrow regeneration could be useful in the management of cancer patients. Patients with solid tumors and bone metastases could be studied to assess bone marrow response to treatment. Patients undergoing myelosuppressive therapy could be studied to assess bone marrow regeneration after treatment.

ACKNOWLEDGMENT

Supported by FISS grant 90/0909.

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