Flare Response Seen in Therapy for Osteomalacia

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We report an interesting case of osteomalacia in which flare response was seen during therapy. The first ^{99m}Tc-methylene diphosphonate bone scan showed increased bilateral and symmetric uptake in the ribs, clavicles and iliac bones. Thoracic CT showed symmetric radiolucent seams (Looser's zones) in both ribs, which were pathognomonic of osteomalacia. After initiation of therapy with vitamin D, the patient's subjective symptoms gradually were relieved. On a second bone scan 4 mo after initiation of therapy, the hot spots in the ribs remained unchanged. Uptake in the bilateral clavicles had become more intense, and new hot spots were recognized in the right lower ribs and left tibia. A third bone scan after 10 mo demonstrated an obvious decrease in the number and intensity of the hot spots. Increased uptakes in the second scan were thought to be a flare response caused by therapy.

Key Words: osteomalacia; flare response; technetium-99m-methylene disphosphonate bone scan

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Osteomalacia is characterized by inadequate mineralization of the organic bone matrix (osteoid) and, on a roentgenogram, osteoid seams (Looser's zones, pseudofractures) are considered pathognomonic of osteomalacia (*1*). Osteoid seams are seen as multiple hot spots on a ^{99m}Tc-methylene diphosphonate (MDP) bone scan, and their symmetrical distribution is considered suggestive of osteomalacia (*2*). Flare response is a phenomenon on ^{99m}Tc-MDP bone scan in which the intensity of the hot spots transiently increases after initiation of therapy of the skeletal metastases (*3,4*). As for non-neoplastic disease, there was a case report of brown tumor due to hyperparathyroidism, which showed a similar phenomenon after parathyroidectomy (*5*). We recently encountered an interesting case of osteomalacia in which flare response was seen on a bone scan performed 4 mo after therapy initiation.

CASE REPORT

A 74-yr-old man was admitted for further examination of generalized bone pain and elevated alkaline phosphatase. His walking was restricted because of lumbago and pain in both lower extremities. He had undergone total gastrectomy 12 yr earlier because of gastric carcinoma. Physical examination revealed no sensory deficit. Laboratory tests revealed elevated alkaline phosphatase of 961 mU/ml (normal 66–220 mU/ml) with a differential fraction indicative of skeletal disease. Serum calcium and serum phosphorus had decreased to 6.6 mg/dl (normal 8.4–10.2 mg/dl) and 2.4 mg/dl (normal 2.5–4.5 mg/dl), respectively. Technetium-99m-MDP bone scan was performed to clarify the causes of the elevated alkaline phosphatase and bone pain. Bilateral and symmetric increased uptakes were noted in the ribs, clavicles and iliac bones (Fig. 1). This distribution of hot spots was thought indicative of osteomalacia rather than skeletal metastases or other pathological conditions (*2*). Thoracic CT with a bone window demonstrated symmetrical radiolucent seams (Looser's zones) in both ribs, which was pathognomonic of osteomalacia (Fig. 2). It was speculated that malabsorption, after total gastrectomy, had caused the osteomalacia. Therapy with vitamin D was initialized.

The pain was relieved gradually by the therapy, and the patient became able to walk as well as before. Serum calcium and phosphorus soon normalized (9.0 mg/dl and 2.9 mg/dl, respectively). Serum alkaline phosphatase, however, had further increased (1309 mU/ml). A second bone scan was performed to evaluate the effectiveness of the therapy about 4 mo after its initiation. Symmetric and bilateral increased uptake in the ribs remained unchanged. Uptake in the bilateral clavicles became more intense, and new hot spots were recognized in the right lower ribs and left tibia (Fig. 3). The meaning of these worsening results was not understood at that time.

Therapy was continued, and a bone scan was repeated about 10 mo after initiation of therapy. By this time, the patient's subjective symptoms had been resolved completely. This third bone scan demonstrated an obvious decrease in the number and intensity of

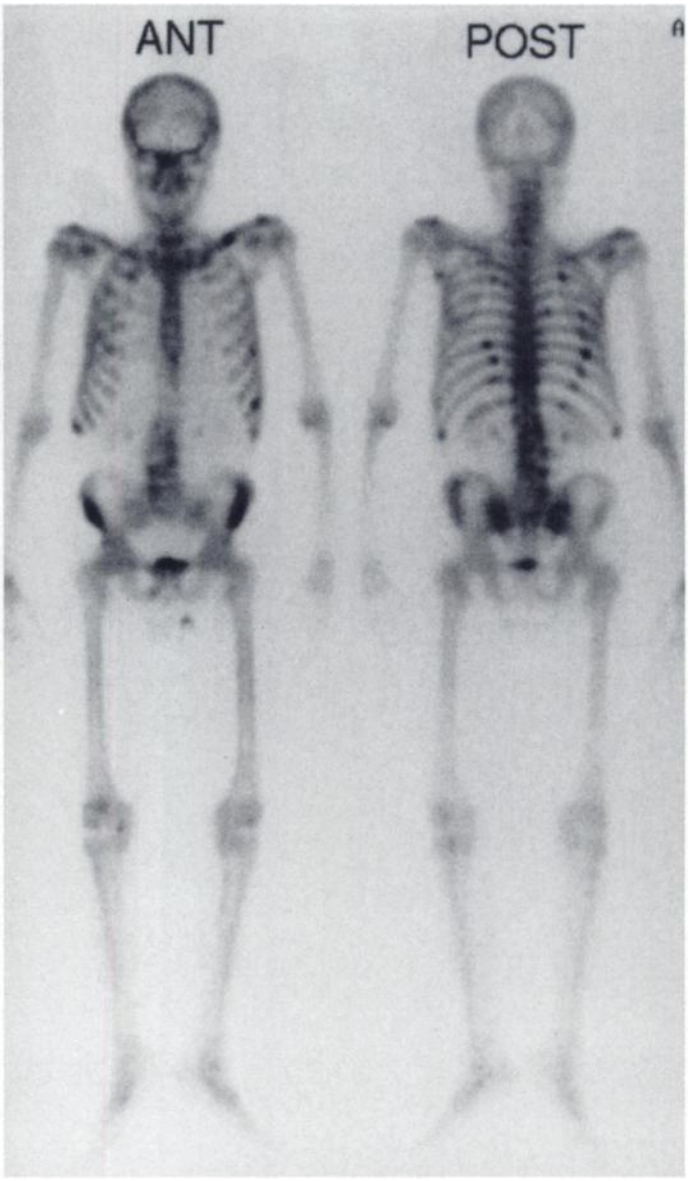

FIGURE 1. Technetium-99m-MDP bone scan demonstrated bilateral and symmetric increased uptake in ribs, clavicles and iliac bones.

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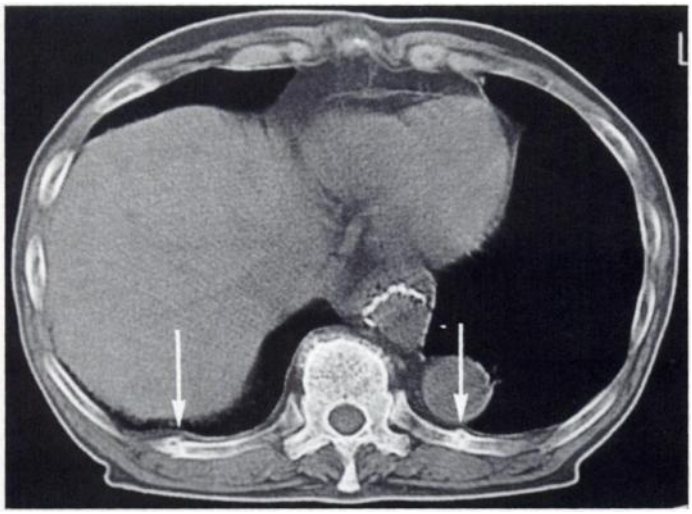

FIGURE 2. CT with bone window setting demonstrated radiolucent seams (Looser's zones) pathognomonic of osteomalacia in both ribs (arrows).

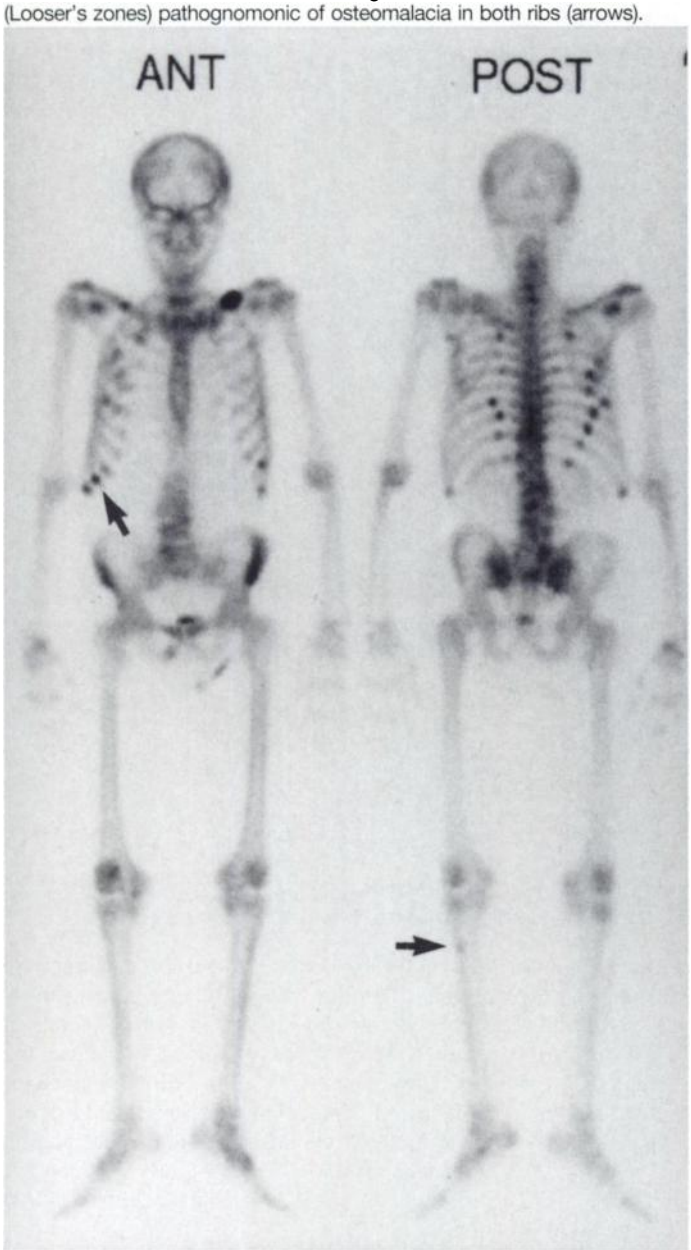

FIGURE 3. Bone scan about 4 mo later shows that increased bilateral and symmetric uptake in ribs remained unchanged. Uptake in bilateral clavicles became more intense, and new hot spots were recognized in right lower ribs and left tibia (arrows).

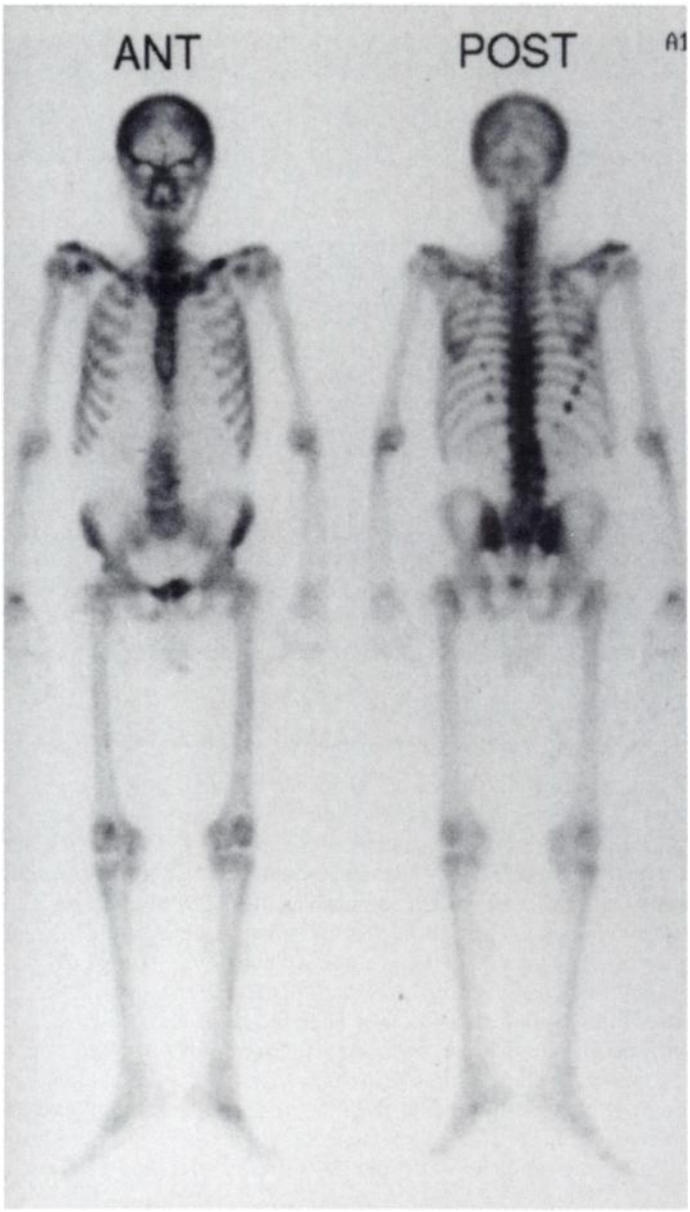

FIGURE 4. Third bone scan demonstrated obvious decrease in number and intensity of hot spots in bilateral ribs, clavicles and both iliac bones. Hot spot in left tibia had disappeared.

hot spots in the bilateral ribs, clavicles and iliac bones. The hot spot in the left tibia had disappeared (Fig. 4). Increased uptakes in the second scan were thought to be a flare response caused by therapy with vitamin D. At this third scan, serum alkaline phosphatase had decreased to 630 mU/ml.

DISCUSSION

Osteomalacia is due to inadequate mineralization of the organic bone matrix (osteoid). It may be caused by vitamin D deficiency (inadequate dietary intake, malabsorption or decreased endogeneous production in the skin due to lack of exposure to sunlight), liver disease, renal disease, hypophosphatasia, tumors of mesenchymal origin or anticonvulsant therapy (*1*). A high bone remodeling rate associated with excessive osteoid, but normal or diminished mineralization, or a low bone remodeling rate with normal osteoid, but diminished mineralization, has been suggested as present in osteomalacia (*6*). Osteoid seams (Looser's zones) are considered pathognomonic of osteomalacia. These are recognized as multiple sites of increased tracer accumulation on ^{99m}Tc-MDP bone scan and

may simulate skeletal metastases (*1,6*). Symmetric distribution, however, is considered a suggestive sign of osteomalacia (*2*).

Flare response is characterized by both increased activity in baseline lesions and new foci of tracer uptake on ^{99m}Tc-MDP bone scan (*3*). It occurs shortly after initiation of therapy and is easily confused with progressive disease (*7*). In reports of flare response in skeletal metastases, it occurs several months after initiation of therapy (*3,8*). This phenomenon has been hypothesized to represent either osteoblastic activity, which is part of the healing reaction to successful therapy, or the manifestation of increased blood flow due to an inflammatory response at the sites of skeletal tumor destruction (*7*).

In the healing process of osteomalacia, mineralization restarts in the osteoid seams. Bone turnover will be activated there, and these reactions may be manifested in a flare response. In the same manner as with cases of skeletal metastases, this phenomenon prevents an exact evaluation of therapy effectiveness. This phenomenon should be considered in therapy for osteomalacia. In a patient with typical radiologic findings before therapy, it is important that therapy be continued even though the bone scan after therapy initiation shows both increased activity in baseline lesions and new foci of tracer uptake.

REFERENCES

1. Velchik MG, Malker PT, Alavi A. Osteomalacia: an imposter of osseous metastasis. *Clin Nucl Med* 1985;10:783–785.
2. Singh BN, Spies SM, Mehta SP, Kesara BA, Quinn III JL. Unusual bone scan presentation in osteomalacia: symmetrical uptake–a suggestive sign. *Clin Nucl Med* 1978;3:292–295.
3. Coleman RE, Mashiter G, Whitaker KB, Moss DW, Rubens RD, Fogelman I. Bone scan flare predicts successful systemic therapy for bone metastasis. *J Nucl Med* 1988;29:1354–1359.
4. Schneider JA, Divgi CR, Scott AM, et al. Flare on bone scintigraphy following taxol chemotherapy for metastatic breast cancer. *J Nucl Med* 1994;35:1748–1752.
5. Hardoff R, Frajewicki V. Bone scintigraphy in hungry bone syndrome following parathyroidectomy. *J Nucl Med* 1996;37:1371–1373.
6. Singh BN, Kesala BA, Mehta SP, Quinn III JL. Osteomalacia on bone scan simulating skeletal metastases. *Clin Nucl Med* 1977;2:181–183.
7. Johns WD, Garnick MB, Kaplan WD. Leuprolide therapy for prostate cancer. An association with scintigraphic "flare" on bone scan. *Clin Nucl Med* 1990;15:485–487.
8. Cosolo W, Morstyn G, Arkles B, Zimet AS, Zalcberg JR. Flare responses in small cell carcinoma of the lung. *Clin Nucl Med* 1988;13:13–16.

Dose Escalation Trial of Indium-111-Labeled Anti-Carcinoembryonic Antigen Chimeric Monoclonal Antibody (Chimeric T84.66) in Presurgical Colorectal Cancer Patients

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Chimeric T84.66 (cT84.66) is a high-affinity ($1.16 \times 10^{11}\ M^{-1}$) IgG1 monoclonal antibody against carcinoembryonic antigen (CEA). The purpose of this pilot trial was to evaluate the tumor-targeting properties, biodistribution, pharmacokinetics and immunogenicity of ^{111}In-labeled cT84.66 as a function of administered antibody protein dose. **Methods:** Patients with CEA-producing colorectal cancers with localized disease or limited metastatic disease who were scheduled to undergo definitive surgical resection were each administered a single intravenous dose of 5 mg of isothiocyanatobenzyl diethylenetriaminepentaacetic acid-cT84.66, labeled with 5 mCi of ^{111}In. Before receiving the radiolabeled antibody, patients received unlabeled diethylenetriaminepentaacetic acid-cT84.66. The amount of unlabeled antibody was 0, 20 or 100 mg, with five patients at each level. Serial blood samples, 24-hr urine collections and nuclear images were collected until 7 days postinfusion. Human antichimeric antibody response was assessed up to 6 mo postinfusion. **Results:** Imaging of at least one known tumor site was performed in all 15 patients. Fifty-two lesions were analyzed, with an imaging sensitivity rate of 50.0% and a positive predictive value of 76.9%. The antibody detected tumors that were not detected by conventional means in three patients, resulting in a modification of surgical management. Interpatient variations in serum clearance rates were observed and were secondary to differences in clearance and metabolic rates of antibody and antibody:antigen complexes by the liver. Antibody uptake in primary tumors, metastatic sites and regional metastatic lymph nodes ranged from 0.4% to 134% injected dose/kg, resulting in estimated ^{90}Y-cT84.66 radiation doses ranging from 0.3 to 193 cGy/mCi. Thirteen patients were evaluated 1–6 mo after infusion for human antichimeric antibody, and none developed a response. No major differences in tumor imaging, tumor uptake, pharmacokinetics or organ biodistribution were observed with increasing protein doses, although a trend toward increasing blood uptake and decreasing liver uptake was observed with increasing protein dose. **Conclusion:** Chimeric T84.66 demonstrated tumor targeting comparable to other radiolabeled intact anti-CEA monoclonal antibodies. Its immunogenicity after single administration was lower than murine monoclonal antibodies. These properties make ^{111}In-cT84.66, or a lower molecular weight derivative, attractive for further evaluation as an imaging agent. Yttrium-90 dosimetry estimates predict potentially cytotoxic radiation doses to select tumor sites, which makes ^{90}Y-cT84.66 also appropriate for further evaluation in Phase I radioimmunotherapy trials. Although clinically important changes in biodistribution, pharmacokinetics and tumor targeting with increasing protein doses of ^{111}In-cT84.66 were not demonstrated, the results do suggest that antibody clearance from the blood is driven by hepatic uptake and metabolism, with more rapid blood clearance seen in patients with liver metastases. These patients with rapid clearance and potentially unfavorable biodistribution for imaging and therapy may, therefore, be a more appropriate subset in which to evaluate the role of administering higher protein doses. This underscores the need to further identify, characterize and understand those factors that influence the biodistribution and clearance of radiolabeled anti-CEA antibodies, to allow for better selection of patients for therapy and rational planning of radioimmunotherapy.

Key Words: chimeric antibody; carcinoembryonic antigen; indium-111; protein dose; radiolabeled antibodies

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