Gallium-67 Scintigraphy in Lymphoma with Bone Involvement

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Both Hodgkin's and non-Hodgkin's lymphoma (NHL) may involve bone. Traditionally, ^{99m}Tc-MDP bone scintigraphy has been used to detect such involvement. In recent years, ^{67}Ga scintigraphy has shown to be useful in monitoring treatment response in lymphoma. Although ^{99m}Tc-MDP has not been found particularly useful for monitoring bone response to cancer treatment, we were interested in whether ^{67}Ga scintigraphy and SPECT could be used to monitor bone involvement with lymphoma. **Methods:** Gallium-67 and ^{99m}Tc-MDP uptake were investigated in 20 patients with lymphoma involving the bone before treatment. Gallium-67 scans were done in 16 patients for monitoring response to treatment in the bone lesions. **Results:** Gallium-67 studies diagnosed bone lesions in 19 of the 20 patients. Technetium-99m-MDP detected bone lesions in all patients investigated. In four patients, uptake by Ga-67 was more intense than ^{99m}Tc-MDP and in another four patients ^{99m}Tc-MDP uptake was more evident. Gallium-67, however, was useful in detecting other regions of involvement in 18 of the 19 patients with soft-tissue lymphoma lesions. Gallium-67 scintigraphy also correctly monitored bone response to treatment in all but one of the 16 patients who had ^{67}Ga scintigraphy after completing therapy. **Conclusion:** Gallium-67 uptake by lymphoma involving the bone can be used to monitor osseous response to treatment.

Key Words: lymphoma; bone; gallium-67; technetium-99m-MDP; Hodgkin's disease

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Bone scintigraphy with ^{99m}Tc-MDP has traditionally been used in the evaluation of bone involvement with cancer. There have been studies which show bone scintigraphy as a useful evaluation of bone involvement in lymphoma (*1–5*). Oncology textbooks recommend screening with ^{99m}Tc-MDP bone scintigraphy when bone involvement is suspected (*6,7*). Past studies maintain that ^{99m}Tc-MDP bone scintigraphy is superior to ^{67}Ga scintigraphy (*1–5*). Only one study describes the value of ^{67}Ga scintigraphy using a small number of patients (*8*). There is, however, no assessment of the value of ^{67}Ga scintigraphy for bone involvement in lymphoma using new, high-resolution and high-sensitivity cameras with high-dose gallium and SPECT. The value of current equipment and techniques for assessing lymphoma involvement of bone is important since ^{67}Ga scintigraphy is now routinely used in selected cancer centers for monitoring response to lymphoma treatment, evaluation of prognosis after treatment and for early detection of recurrence (*9–17*). This information cannot be provided by CT. We were interested in whether ^{67}Ga is taken up by bone lesions in lymphoma before treatment so that it could be used to monitor response after treatment.

We tested the utility of ^{67}Ga scintigraphy in bone involvement before treatment in 20 patients and compared it to ^{99m}Tc bone scintigraphy. We also determined whether ^{67}Ga scintigraphy would provide a suitable technique to monitor response to treatment of lymphoma in bone.

MATERIALS AND METHODS

Twenty-five patients with lymphoma, who are part of an ongoing study to evaluate the role of ^{67}Ga in lymphoma (*9,11,12,17*), had a bone disease. Two of these patients, with evidence of lymphoma involving lymph nodes and bone, had normal ^{67}Ga scintigraphy in both regions. They were considered to have a nongallium-avid lymphoma and were excluded from the study group. Another three patients were excluded because their ^{67}Ga study was done after surgical biopsy of suspected sites of skeletal disease. Criteria for inclusion in the study were: uptake of ^{67}Ga in diseased lymph nodes and evidence of bone involvement as determined by CT, x-rays or biopsy. The study group included 20 lymphoma patients with ^{67}Ga uptake in lymph nodes, CT and x-ray evidence of bone involvement. This study examined the value of ^{67}Ga scintigraphy in assessing tumor involvement of the bone in patients who had ^{67}Ga uptake in lymph nodes and soft tissue. They were included irrespective of whether they showed ^{67}Ga uptake in the involved bone.

There were 10 male and 10 female patients, with an average age of 34.6 yr (range 7–77 yr). Eight patients suffered from Hodgkin's disease and 12 from non-Hodgkin's lymphoma (NHL), intermediate or high grade, according to the Working Formulation. In one patient, primary bone lymphoma was first diagnosed by biopsy of a bone lesion yet CT in the patient showed involvement of other bone sites, which were evaluated by ^{67}Ga in this study. The other 19 patients had secondary bone involvement, 16 had CT, two had both CT and x-rays and one had only x-rays. Gallium-67 scintig-

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raphy, ^{99m}Tc-MDP bone scintigraphy, x-rays, CT and biopsy were all done within a mean period of 1 mo. Clinical response to treatment was based on the accepted oncological criteria (*9–14*). A complete response on ^{67}Ga scintigraphy was indicated when abnormal uptake in the bone completely disappeared after treatment completion. Gallium-67 uptake after treatment was compared to oncological diagnosis after treatment as well as follow-up results. Scintigraphic uptake was determined by consent of three nuclear medicine physicians (R.B.-S., O.I. and D.F.). Gallium-67 scintigraphy was done using previously described techniques (*11,12,17*). Adult patients received 8 mCi (296 MBq) of ^{67}Ga-citrate intravenously and children received 75 uCi (2.77 MBq) per kg of body weight. Scintigraphy was performed on all patients after 48 hr and repeated seven days following injection. When deemed necessary, for clearance from the abdomen, images were also obtained 14 days after injection. The images were obtained with large, or very large rectangular field of view digital SPECT cameras or with a dual-head camera (Apex 415-ECT, SP-6HR ECT or Helix, Elscint, Haifa, Israel). Triple-energy peaks of 93, 184 and 300 keV and a parallel-hole, medium-energy collimator (APC-5) were used. A collimator designed for ^{67}Ga (HPC-5) was used with the dual-head camera. For planar scintigraphy, anterior and posterior views were obtained and 500 to 1000 Kcts were accumulated for each view. When the dual-head camera was used, whole-body scanning was done in one pass for 20 min at 48 hr and for 26 min at 7 days. SPECT imaging was usually performed at 48 hr after the planar study. The data acquisition protocol included a 360° rotation, with 60 projections, 6° apart; 3.5–8 × 10^6 counts were acquired per study. A matrix of 64 × 64 and a Hanning filter were used. Data were reconstructed using an SP-1 or XP-1 (Elscint, Haifa, Israel) computer. Tomographic images were obtained in the transaxial, coronal and sagittal planes. Bone scintigraphy was performed 3 to 4 hr after the injection of 20 mCi–25 mCi ^{99m}Tc-MDP. For each view of the whole body, 1000 Kcts were collected, including the limbs. Whole-body scintigraphy with the dual head camera lasted for 20–25 min depending on patient size. SPECT images were done when spine involvement with lymphoma was suspected or when a lesion could not be properly evaluated on planar imaging. Gallium-67 images were evaluated and compared to ^{99m}Tc-MDP scintigraphy before treatment. Observers determined whether there was bone uptake and if present was it of the same intensity or higher in the gallium or bone studies.

RESULTS

Nineteen patients had bone involvement secondary to nodal involvement and one patient had primary lymphoma of the bone. Eight patients had bone involvement in one skeletal site, six in two skeletal sites, one in three skeletal sites of disease and five in four sites of bone involvement. There were five patients with six sites of involvement of the lumbar and thoracic spine, six patients with nine sites of involvement in the pelvis, six patients with nine sites of disease in the thoracic cage, five patients with seven sites of involvement in the skull and five patients with 12 sites of disease in the appendicular skeleton (Table 1).

Nineteen of the 20 patients with bone involvement showed abnormal bone uptake on ^{67}Ga scintigraphy. One patient showed ^{67}Ga uptake in involved nodes, but not in the bone lesion. In another patient, ^{67}Ga scintigraphy showed the bone lesion, but was false-negative in the sites of soft-tissue lymphoma. In the other 18 patients, ^{67}Ga was positive, both in the bone and the soft tissue sites of disease. Technetium-99m-MDP bone scan was positive in all bone lesions. In four patients, ^{99m}Tc-MDP uptake in the bone lesions was lower than that of ^{67}Ga (Figs. 1 and 2) and in four patients ^{67}Ga uptake in the bone was of lower intensity than that of ^{99m}Tc-MDP. Out of the 19 patients with positive gallium uptake in bone lesions, 12 patients had a complete response as judged by oncological criteria and by follow-up (*9–15*). Gallium-67 in 11 of these patients returned to normal. In one patient it remained false-positive at the end of treatment. Four patients did not respond to treatment and were defined as nonresponders by oncological criteria. Gallium-67 bone uptake in these four patients remained abnormal after completing the treatment. Three other patients did not have ^{67}Ga scintigraphy after completing therapy (one patient died shortly after diagnosis and two did not have routine oncological follow-up). The mean follow-up period was 30.5 mo.

TABLE 1
Bone Involvement in 20 Patients with Lymphoma

Region of bone involvement	Patient no.*	Localization/ no. sites	Total no. of sites*
Spine	5	L-4/1 L-3/2 T-8/1 T-1/2	6
Pelvis	6	Sacrum/3 Ilium/3 Pubis/2 Acetabulum/1	9
Thoracic cage	6	Sternum/3 Clavicle/2 Ribs/4	9
Skull	5	Maxilla/5 Mandible/1 Parietal/1	7
Long bones	5	Femur/3 Tibia/4 Humerus/5	12

*Twelve of the 20 patients with bone involvement on CT or x-rays had more than one site of involvement.

DISCUSSION

Osseous involvement in both Hodgkin's disease and NHL occurs in about 10%–15% of patients at some time during the course of the disease. As many as one-third of the patients with Hodgkin's disease may show skeletal involvement during the disease process. However, primary involvement of the bone at presentation is rare (*18,19*). Secondary bone involvement occurs either per continuitatum extension of the disease, or through hematogenous dissemination. It can occur at any stage of the disease and

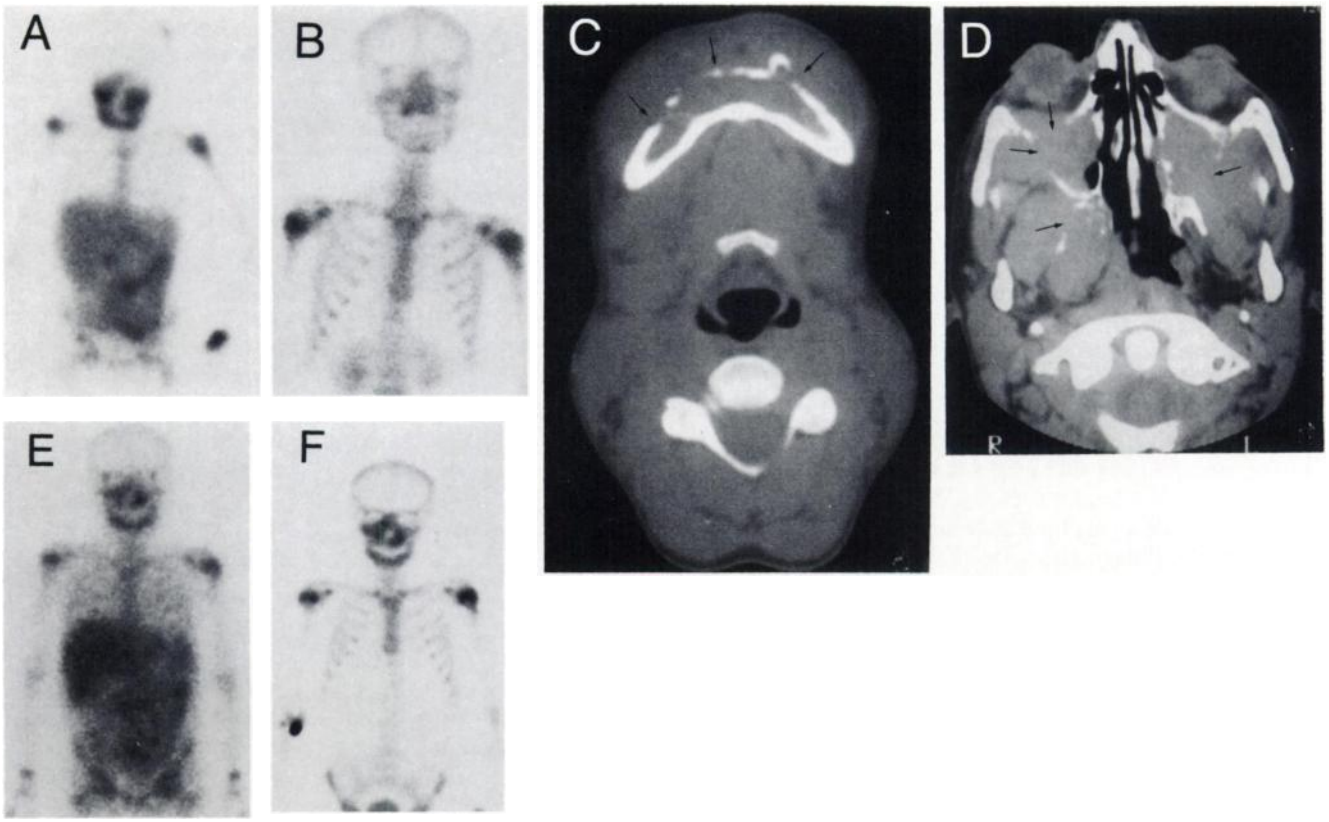

FIGURE 1. Gallium-67 and bone scintigraphy in a 10-yr-old male with Burkitt's lymphoma involving the bones of the face, the maxillary sinus and the left humerus. (A) Pretreatment ^{67}Ga scintigraphy shows involvement of the mandibles, maxillary bone and sinus, parietal bone and left humerus. (B) Bone scintigraphy shows the same lesions although less intense, particularly in the mandible. (C) Axial CT scan at the level of the mandible, shows a lytic lesion involving the anterior cortex. An extraosseous soft tissue mass (arrows) is also seen. (D) CT at the level of the maxillary sinuses shows a large mass in both sinuses destroying the right and left maxillary bones, and the right pterygoid apophysis (arrows). Note protrusion of the mass into the right orbit. (E) Gallium-67 scintigraphy during treatment showing marked reduction in uptake in all sites of disease. (F) Bone scintigraphy during treatment shows increased uptake, especially in the mandible, as compared to the pretreatment study.

does not necessarily have the ominous implication of bone marrow involvement. Long-term disease-free survival is possible with proper treatment. In NHL, 7% to 25% of patients develop bone findings at some point during their clinical course. About 4% of all patients present with primary skeletal lesions (*19,20*). In Hodgkin's disease, the appendicular skeleton is more often affected than the axial skeleton (56% versus 44%) (*5*). NHL affects the axial skeleton more often than the appendicular skeleton (79% versus 21%) (*5,20*). Primary lymphoma of bone involves the long bones most often (*6*) and is mainly of the large-cell group (*6*). The clinical presentation of bone lymphoma is pain and a soft-tissue mass. Bone involvement is usually diagnosed by x-rays, CT and MRI (*6,7*).

The mechanism of ^{67}Ga uptake in normal bone is not clear and the individual differences in uptake between patients are very large (*21–24*). Uptake in normal bone is partly due to ^{67}Ga being a bone-seeking agent. It is taken up to an extent by the same mechanism of adsorption of the organic phosphates, used for bone scintigraphy (*21, 24–31*). The fact that ^{67}Ga scintigraphy turns normal in response to successful lymphoma treatment (*9–11*) probably indicates a different mechanism of uptake in lymphoma. Mechanism for ^{67}Ga uptake in lymphoma involving the bone is probably more similar to that of the uptake in lesions in soft tissue elsewhere in the body than that of ^{99m}Tc-MDP in the bone.

It has been suggested that bone scintigraphy, CT, and in selected cases, biopsy should be performed for diagnosis of lymphoma in bone (*1–7,20*). Not every bone region suspected of being involved with lymphoma should be biopsied, but x-rays and CT can be used for specific diagnosis. The value of bone and ^{67}Ga scintigraphy is in screening the whole body. This is not routinely done when x-rays and CT are used. Orzel et al. (*5*) reviewed lymphoma involving the bone for the results of ^{67}Ga and ^{99m}Tc-MDP bone scintigraphy. They found that bone scintigraphy detected bone involvement in 95% of their patients while ^{67}Ga detected bone involvement in only 44% of their patients. Their technique had, however, a number of deficiencies. They used a dose of only 5 mCi of ^{67}Ga and, in some of the patients, old equipment was used. It is also not clear from their paper what the gold standard was for the diagnosis of bone involvement; it appears that the bone scan was used as the standard to indicate that the bone was involved with disease. Gallium-67 scintigraphy was compared to ^{99m}Tc-

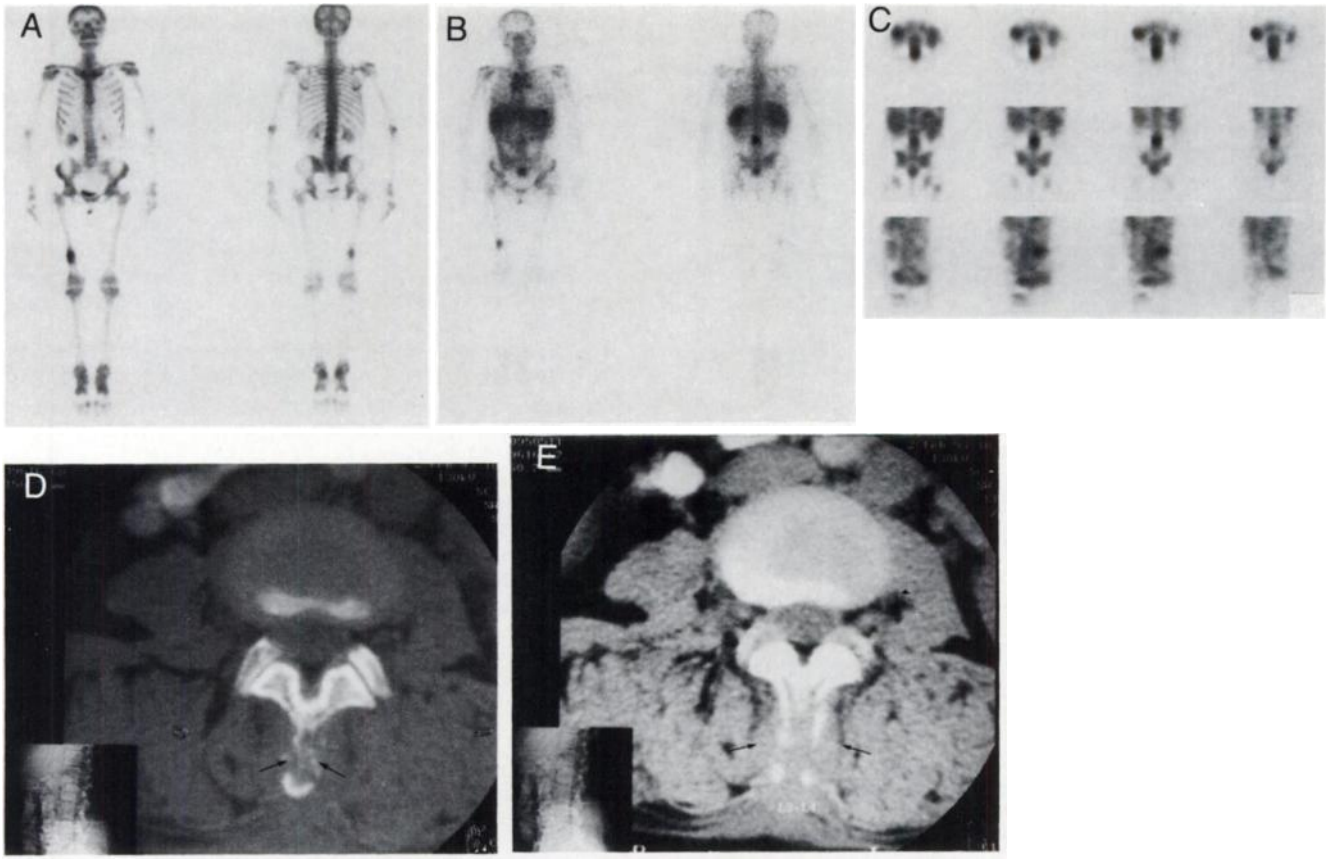

FIGURE 2. Gallium-67 and bone scintigraphy in a 39-yr-old female with diffuse large-cell immunoblastic lymphoma who complained of low back pain a short time after completing chemotherapy with Promace/MOPP. (A) Bone scintigraphy shows only slight abnormal uptake in the L-3 vertebra and the distal third of the right femur. (B) Planar ^{67}Ga scintigraphy shows intense abnormal uptake in the L-3 vertebra and abnormal uptake in the right femur and sacrum. Pathological uptake in the mediastinum is also shown. (C) Gallium-67 SPECT images in the transaxial, coronal and sagittal sections shows the lesion in the spinous process of L-3. CT at the level of the third lumbar vertebra using bone (D) and soft-tissue (E) windows shows symmetric lysis of the spinous process and a bilateral, paravertebral soft-tissue mass (arrows). CT (not shown) also confirmed the lesions shown on ^{67}Ga scintigraphy in the femur, sacrum and mediastinum.

MDP bone scintigraphy if there was no significant clinical intervention within 2 wk of the bone scan (*5*). We now know, however, that even one course of chemotherapeutic treatment can reverse positive gallium uptake. Therefore, the comparison of bone and gallium scans under such circumstances may not be valid.

The use of better techniques, i.e., higher ^{67}Ga dose, sensitive cameras, especially dual head cameras, SPECT and performance of repeat studies, along with the understanding that ^{67}Ga is a viability agent, have recently made ^{67}Ga scanning an important tool in the management of lymphoma (*9–17*). Results of this study indicate that lymphoma involving the bone demonstrates ^{67}Ga uptake; this uptake may be used to monitor response to treatment in such lesions. All but one of the bone lesions were seen on ^{67}Ga scintigraphy in Ga-avid lymphomas. In four patients, uptake seemed lower than in bone scintigraphy, but in another four patients uptake was higher than on the bone scan (Figs. 1 and 2). Gallium-67 scintigraphy was able to diagnose concomitant soft-tissue involvement, which is not possible when using bone scintigraphy (Fig. 2). It has been suggested that serial-diphosphonate bone scintigraphy is useful to evaluate patient response to treatment (*2*). Yet this is not possible after early treatment when it is necessary to determine complete patient response (*16*). Although diphosphonate uptake in bone after treatment was not investigated in this study, bone scintigraphy in metastatic bone lesions in other cancers remains abnormal for a period after response to treatment has been achieved. Although ^{67}Ga is to some extent a bone-seeking agent, this study shows that it is nevertheless highly appropriate in monitoring bone response to treatment (Fig. 1). Gallium-67 becomes negative when the patient achieves a complete response to treatment. Apparently the lymphoma seeking properties of ^{67}Ga are more pronounced than those of its bone seeking properties. We were not able to find literature on the value of CT in monitoring bone lymphoma after treatment.

Gallium-67 scintigraphy is not recommended here as a diagnostic test of bone involvement and should only be used in ^{67}Ga-avid lymphoma. For the initial diagnosis, x-rays, CT or MRI showing bone lesions in histologically proven lymphoma should be used. Gallium-67 evaluation of bone involvement in lymphoma is important for determining the effect of therapy and whether the patient has achieved a complete response.

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