Ectopic Hematopoietic Bone Marrow in the Appendicular Skeleton After Trauma

Achim Kaim, Peter Ochsner, Thomas Maurer, Gernot Jundt and Jan Mueller-Brand
Institutes of Nuclear Medicine, Diagnostic Radiology and Pathology, University Hospital Basel, Basel; and Department of Orthopedic and Trauma Surgery, Kantonsspital Liestal, Switzerland

Methods: Combined bone scanning and immunoscintigraphy (IS) with ^{99m}Tc-monoclonal antigranulocyte antibodies were performed in two patients with suspected reactivation of chronic osteomyelitis of the lower extremity. Because bone scanning and IS were strongly positive, both patients underwent surgical intervention. **Results:** Macroscopic findings did not show purulent infection and microbiologic results remained negative, but histology revealed unexpected ectopic bone marrow, explaining the strong uptake on IS. One patient exhibited active hematopoietic bone marrow at the former fracture site of the tibial bone. The second patient presented with interspersed bone marrow in the cortical bone of the femoral diaphysis after several intramedullary surgical procedures. **Conclusion:** Unexpected ectopic hematopoietic marrow may occur in the appendicular skeleton after trauma and repeated surgical interventions. The bone marrow shows a physiologic uptake with IS and may be misinterpreted as granulocyte accumulation due to infection. This may lead to false-positive diagnosis in cases of suspected osteomyelitis.

Key Words: immunoscintigraphy; radionuclide imaging; bone marrow; trauma

J Nucl Med 1998; 39:1980–1983

The diagnosis of chronic post-traumatic osteomyelitis (OM) represents a particular challenge for radiology and nuclear medicine. Bone necrosis with pathologic fracture, lung embolism and sepsis are some of its complications, and the disease frequently leads to disability and reduced life quality in a young patient group. Nuclear medicine has proven to be very useful in the investigation of chronic bone infection. Bone scanning has a high sensitivity and should be followed by a more specific method. In recent years, immunoscintigraphy (IS) with ^{99m}Tc-labeled monoclonal antigranulocyte antibodies (MAbs) has been accepted as an accurate method for the detection of infected foci in the appendicular skeleton (*1–6*). Problems in the diagnosis of infection appear in areas with hematopoietically active bone marrow such as the spine, pelvis, ribs, sternum, skull and the proximal femora and humeri because precursor cells of the granulopoietic system, such as promyelocytes, express the same specific surface antigen and also take up the ^{99m}Tc-MAb label. A physiologic uptake in the bone marrow occurs and infection causes nonspecific photopenic zones due to bone marrow destruction.

We describe two cases of suspected post-traumatic OM of the lower extremities, in whom unexpected hematopoietic active bone marrow showed a physiologic uptake and was misinterpreted as granulocyte accumulation due to activated infection.

Received Nov. 6, 1997; revision accepted Jan. 30, 1998.
For correspondence or reprints contact: Achim Kaim, MD, Institute of Nuclear Medicine, University Hospital Basel, Petersgraben 4, CH-4032 Basel, Switzerland.

MATERIALS AND METHODS

Radiopharmaceuticals

The antigranulocyte antibody used for IS was a murine monoclonal antibody (BW250/183), supplied by Behringwerke AG (Zurich, Switzerland). The antibody is an immunoglobulin of the IgG isotype and binds to the epitope NCA 95 on the surface of human granulocytes. The antibody was reduced with stannous(II) chloride solution and labeled with ^{99m}Tc. After an incubation period of 10 min, 555 MBq of the antibody solution (equivalent to 0.5 mg of the antibody) were intravenously injected into the patient. Serum was obtained before and 3 wk after injection to determine titer of human antimouse antibodies (HAMAs). None of the patients developed HAMAs, and no side effects or adverse reactions were observed.

For the ^{99m}Tc-diphosphonate bone scan, 3,3-diphosphono-1,2-propanedicarboxyl acid tetrasodium salt (Hoechst, Switzerland) was used. It was labeled with an average of 740 MBq ^{99m}Tc.

Imaging Modalities

Both patients first underwent a quantitative three-phase bone scan followed by IS, with an interval of 2 days to 1 wk. After injection of ^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxyl acid tetrasodium salt, 20 5-sec images were immediately registered, and another 60-sec image was taken at 5 min. Five hundred-kilocount planar spot images were obtained 3 hr after injection and stored on computer using a 256 × 256 matrix.

Immunoscintigraphy was performed 17 hr postinjection. Planar spot images of the suspected area in at least two projections were obtained. Five hundred-kilocount images with a 256 × 256 matrix were recorded. Additionally, whole-body images were obtained.

Imaging was performed with a Siemens DIACAM gamma camera equipped with a low-energy, high-resolution collimator connected to a dedicated computer system (Icon; Siemens, Zurich, Switzerland).

Patients

Case 1. A 27-yr-old woman suffered from an 10-yr history of chronic and recurrent OM of the tibia. The initial spiral fracture of the tibial diaphysis was treated by plate osteosynthesis. Infected pseudarthrosis occurred and was treated by debridement, local antibiotics and external fixation. One year later, a sequestrum was removed, and the further clinical course was favorable. However, over the next 2 yr, minor pain increased and led to another investigation. Laboratory findings [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count] were normal. Plain x-irradiation showed sclerosis and thickening of cortical bone at the former fracture site without progression. In the MRI, the fatty marrow at the suspected site was replaced (low signal intensity on T1-weighted images), but neither edema nor gadolinium enhancement was shown. A late bone scan (3 hr after injection) demonstrated increased bone metabolism, and subsequent IS showed a strong accumulation of ^{99m}Tc-MAb (Fig. 1A–C). On the basis of the scintigraphic results, reactivation of OM was

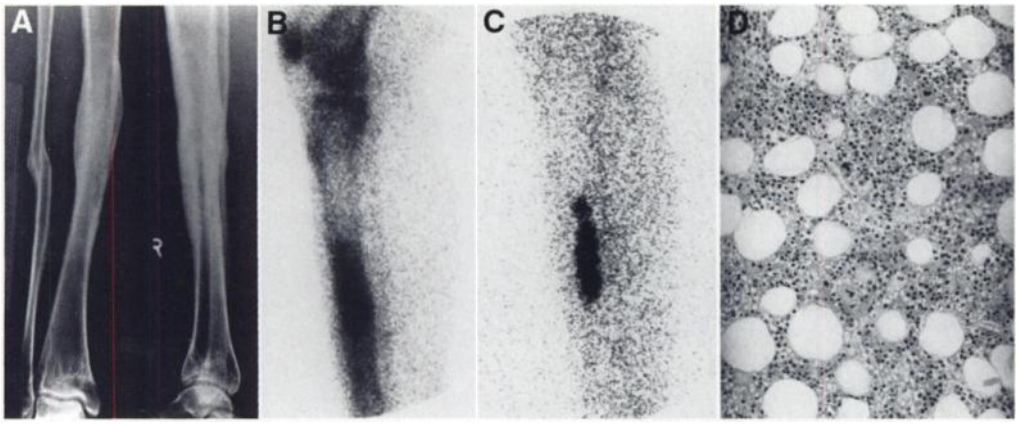

FIGURE 1. False-positive IS finding due to ectopic hematopoietic bone marrow in 27-yr-old woman with 10-yr history of recurrent OM. (A) Radiograph (anteroposterior, lateral view) of tibia shows sclerosis and thickening of cortical bone at former fracture site. (B) Late bone scan (lateral view) reveals increased bone metabolism. (C) Strong accumulation of ^{99m}Tc-MAb is demonstrated on IS. (D) Histology of medullary cavity reveals hematopoietic bone marrow. No signs of inflammation.

diagnosed, and surgical intervention was performed. Macroscopically, no evidence for purulent infection was found, and tissue specimens were taken. Histology did not reveal clusters of granulocytes, as expected, but showed large areas of hematopoietic bone marrow that had been located in the medullary cavity (Fig. 1D). Microbiologic results remained negative.

Case 2. A 66-yr-old man suffered from a complex multifragmentary fracture of the femoral diaphysis 34 yr ago, which was treated by intramedullary nailing. During the next 30 yr, he had five operations, with removal of sequestra due to recurrent OM. Four years ago, treatment by intramedullary suction irrigation drainage was performed. Seven months before admission, he was treated by intramedullary reaming due to infection with *Staphylococcus aureus*. The persisting complaints of the patient led to further investigations. Laboratory results (ESR, CRP and WBC count) were normal. Plain x-irradiation was followed by a combined bone scan and IS. The bone metabolism of the complete femoral diaphysis was increased. Immunoscintigraphy showed an accumulation of ^{99m}Tc-MAb in the mid-femoral diaphysis. The accumulation was along the cortical and periosteal bone, had a parallel and linear distribution and spared the medullary cavity (Fig. 2A–C). Fenestration of cortical bone at the suspected site and intramedullary reaming were performed. Macroscopically, no purulent infection was found. Histology showed the cortical bone to be interspersed with hematopoietic marrow, and no evidence for a granulocytic inflammation was found (Fig. 2D). Intraoperative microbiology was negative.

RESULTS

Both patients had strongly positive bone scans and IS that was misinterpreted as granulocyte accumulation due to activated OM and led to surgical intervention. Microbiologic results were negative, and histology revealed ectopic hematopoietic active bone marrow explaining the strong uptake on IS. Case 1 exhibited bone marrow at the former fracture site of tibial bone, and Case 2 presented with interspersed bone marrow in the cortical bone of the femoral diaphysis after several intramedullary procedures. The findings are illustrated and summarized in Figures 1 and 2.

DISCUSSION

Radiolabeled autologous white cells are still considered the gold standard in nuclear imaging of infected sites. However, the examination requires time-consuming ex vivo blood handling techniques and special training and represents an infection risk to both laboratory personnel and patients. Technetium-99m-MAb binding granulocytes show a quite similar in vivo distribution to that of radiolabeled granulocytes and allow the detection of granulocyte accumulation in the appendicular skeleton. The advantage of ^{99m}Tc-labeled MAb is the simplicity of the labeling process of technetium with the antibodies and the in vivo labeling of granulocytes. The antibodies are directed against the myeloid-specific surface antigene *NCA-95*, expressed by granulocytes. However, there are several situations that may lead to false diagnosis. Technical problems, such as incomplete labeling of the MAb with ^{99m}Tc; altered biodistribution in follow-up studies due to the induction of HAMAs (*2,7*); and nonpurulent diseases, such as fractures, osteosarcoma, eosinophilic granuloma and Paget's disease (*3,8*) may rarely cause diagnostic errors.

Here, we describe two cases with unexpected distributed hematopoietic bone marrow in the appendicular skeleton, which led to a false-positive diagnosis in the investigation of chronic posttraumatic OM. The strongly positive IS in both cases is explained by the labeling of the promyelocytes with ^{99m}Tc-MAb, which express the identical specific surface antigene *NCA-95*, as do granulocytes. The functioning marrow is normally confined to the vertebrae, pelvis, ribs, sternum scapulae, skull and proximal portions of the humeri and femora in adults, but there is considerable individual variation. Occasionally, microscopic red marrow can extend to the tubular bones of the appendicular skeleton in some adults (*9*). The sites of former fetal hematopoiesis, such as the distal femurs and the tibial bones, may be reactivated by underlying diseases characterized by production of one or more types of blood cells and stress disorders, such as chronic anemia, acquired heart diseases with chronic heart failure, tumors, burns and trauma (*9–11*).

Ectopic myelopoiesis has been observed in several circumstances combined with osteogenesis. Animal studies revealed myelopoiesis in ectopic bone formation after lesions to the central nervous system, and similar phenomena were postulated for paraosteoarthropathies within the scope of severe trauma, burns and spinal cord injuries (*12*). Repeated femoral curettages in mice experiments demonstrated the capacity of stromal precursor cells for formation of hematopoietic microenvironment in bone (*13*). Analysis of mesenchymal stem cell potential provided evidence of the relationship of osteogenesis to angiogenesis and myelopoiesis (*14*). Implantation of an orthopedic joint prosthesis was found to be a cause for alterations in the distribution of otherwise normal bone marrow (*15*). Active myelopoiesis and myeloid precursors were detected in the bone marrow adjacent to rheumatoid arthritis joints (*16*).

This clinical series reports the appearance of ectopic bone marrow in suspected chronic OM after trauma and the subsequent misinterpretation of combined bone scan and IS. The differences in the distribution of the hematopoietic marrow in the two presented cases and the patients' histories let us postulate two different hypothesis for the genesis of this phenomenon. In Case 1, the hematopoietic marrow was located

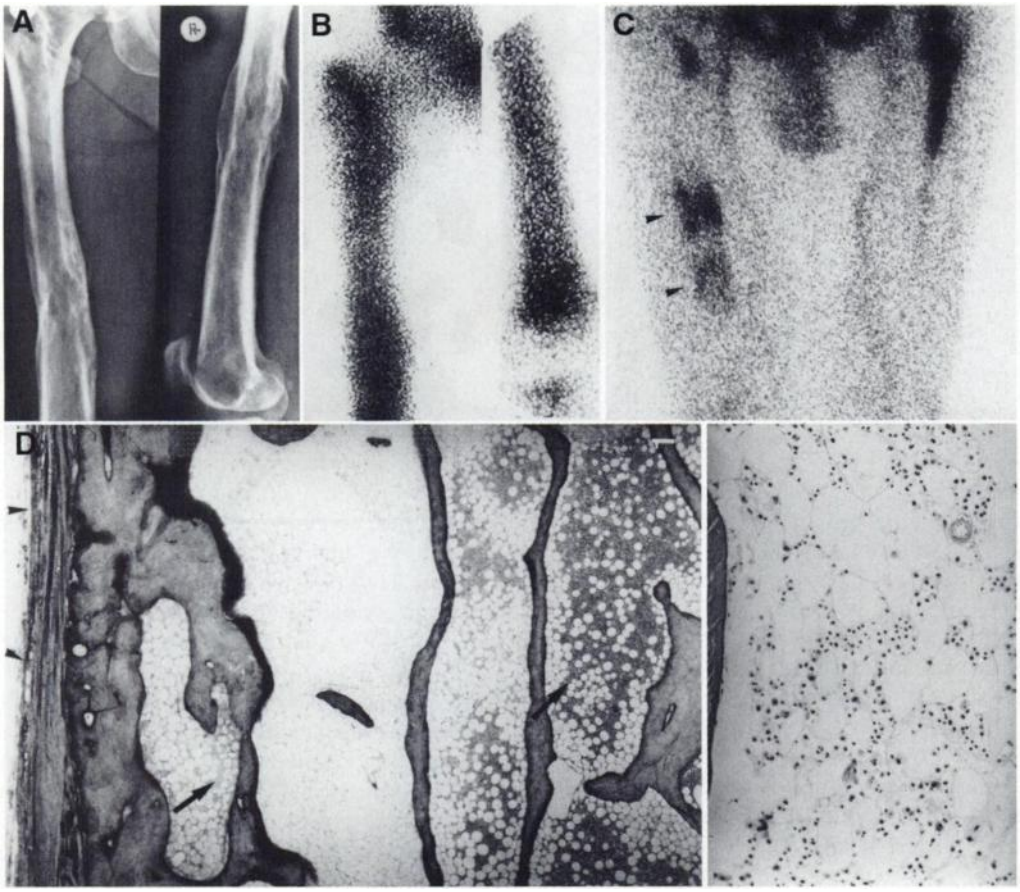

FIGURE 2. False-positive finding in 66-yr-old man with fracture of femoral diaphysis that occurred 34 yr ago. Patient had a history of recurrent chronic OM and repeated surgery, with last intervention being 7 mo ago (intramedullary reaming). (A) Radiograph (anteroposterior, lateral view) of femoral diaphysis shows post-traumatic changes with laminated appearance of cortical bone and periosteal bone formation. (B) Late bone scan (anterior) reveals increased bone metabolism of complete femoral diaphysis. (C) Immunoscintigraphy (anterior) demonstrates accumulation of ^{99m}Tc-MAb in mid-femoral diaphysis along periosteal and cortical bone with sparing of medullary cavity (arrowheads). (D) Histologic overview (left) shows subperiosteal cortical bone with laminated appearance and interspersed hematopoietic and fatty marrow (arrow). Arrowheads, periosteum. Magnification view (right) demonstrates all three cell lines of hemopoiesis.

in the medullary cavity of the tibia and limited to the former fracture site. Bone metabolism was increased on bone scan. Several factors are known to influence the survival, proliferation and functional activation of myeloid hematopoietic cells: macrophage colony-stimulating factor (CSF), granulocyte CSF, granulocyte–macrophage CSF and interleukin 3 (*17*). Other cytokines, including interleukins 1, 5, 6 and 11 are also considered to have an effect on these processes (*18*). Bone morphogenetic protein was observed to stimulate neogenesis of hematopoietical bone marrow in ectopic bone (*19*). Some of these mediators might be released due to a chronic inflammatory stimulus and induced osteogenesis and myelopoiesis in the stromal cells of the peripheral skeleton. The second patient presented with interspersed bone marrow in the cortical bone that was arranged in layers between the architecture of the remodeled cortical bone. He had a history of several surgical manipulations in the medullary cavity of the femur. This raises the possibility that active bone marrow had been displaced from the proximal femur to the diaphyseal location during the various intramedullary surgical procedures. The bone marrow was integrated into the cortical bone in the course of endosteal remodeling and explained the intracortical uptake on IS.

One potential implication of our findings is that abnormal peripheral skeleton studies with IS might need to be confirmed as true-positive results by bone marrow imaging with ^{99m}Tc-sulfur colloid (SC). Until now, colloid scintigraphy has not been considered a complement to IS. The use of marrow imaging with ^{99m}Tc-SC was proposed as a complement to leukocyte imaging to distinguish infected joint prosthesis from periprosthetic marrow distribution (*8,20*). Even if performing colloid scintigraphy were necessary, IS would still be a more convenient and safer diagnostic method than leukocyte imaging. Therefore, further prospective studies that use complementary bone marrow imaging in suspected chronic OM with positive IS are being planned to investigate the frequency of unexpected bone marrow appearance and its potential causes in patients with suspected peripheral chronic OM.

CONCLUSION

Ectopic hematopoietic bone marrow may occur in the appendicular skeleton after trauma. Immunoscintigraphy shows a strong accumulation of ^{99m}Tc-MAb and may lead to a false-positive diagnosis of active infection in cases of suspected OM. Because of this pitfall, correlative bone marrow imaging with ^{99m}Tc-SC is recommended for cases with increased skeletal uptake on IS.

REFERENCES

1. Sciuk J, Brandau W, Vollet B, et al. Comparison of ^{99m}Tc polyclonal human immunoglobulin and ^{99m}Tc monoclonal antibodies for imaging chronic osteomyelitis. First clinical results. *Eur J Nucl Med* 1991;18:401–407.
2. Steinstaesser A, Oberhausen E. Granulocyte Labelling Kit BW 250/183. Results of the European Multicenter Trial. *Nucl Med* 1996;35:1–11.
3. Hotze AL, Briele B, Overbeck B, et al. Technetium-99m-labeled antigranulocyte antibodies in suspected bone infections. *J Nucl Med* 1992;33:526–531.
4. Reuland P, Winkler KH, Heuchert T, et al. Detection of infection in postoperative

patients with ^{99m}Tc-labeled monoclonal antibodies against granulocytes. *J Nucl Med* 1991;32:2209–2214.
5. Scheidler J, Leinsinger G, Pfahler M, Kirsch CM. Diagnosis of osteomyelitis. Accuracy and limitations of antigranulocyte antibody imaging compared to three-phase bone scan. *Clin Nucl Med* 1994;19:731–737.
6. Kaim A, Maurer T, Ochsner P, Jundt G, Kirsch E, Mueller-Brand J. Chronic complicated osteomyelitis of the appendicular skeleton: diagnosis with technetium-99m-labelled antigranulocyte antibody-immunoscintigraphy. *Eur J Nucl Med* 1997; 24:732–738.
7. Hyams D, Reynolds JC, Carrasquillo JA, et al. The effect of circulating antimurine antibody on the pharmacokinetics and biodistribution of injected radiolabeled monoclonal antibody [Abstract]. *J Nucl Med* 1986;27:922.
8. Oyen WJG, van Horn JR, Claessens AMJ, Sloof TJJH, van der Meer JWM, Corstens FHM. Diagnosis of bone, joint and joint prosthesis infection with ^{111}In-labeled nonspecific human immunoglobulin. *Radiology* 1992;182:195–199.
9. Kricun ME. Red-yellow marrow conversion: its effect on the location of some solitary bone lesions. *Skel Radiol* 1985;14:10–19.
10. Johnell O, Hulth A. The mitotic activity of bone marrow and thymus after combined antigenic challenge and trauma. *Acta Orthop Scand* 1979;50:713–715.
11. Van Dyke D, Harris N. Bone marrow reactions to trauma. Stimulation of erythropoietic marrow by mechanical disruption, fracture or endosteal curettage. *Blood* 1969;34:257–275.
12. Brown H, Ehrlich HP, Newberne PM, Kiyoizumi T. Paraosteoarthropathy—ectopic ossification of healing tendon about the rodent ankle joint: histologic and type V collagen changes. *Proc Soc Exp Biol Med* 1986;183:214–220.
13. Chertov JL, Gurevitch OA. Self-maintenance ability and kinetics of hemopoietic stroma precursors. *Cell Tissue Kinet* 1980;13:535–541.
14. Caplan AI. Cartilage begets bone versus endochondral myelopoiesis. *Clin Orthop* 1990;261:257–267.
15. Palestro CJ, Swyer AJ, Kim CK, Goldsmith SJ. Infected knee prosthesis: diagnosis with ^{111}In leukocyte, ^{99m}Tc sulfur colloid and ^{99m}Tc MDP imaging. *Radiology* 1991;179:645–648.
16. Kotake S, Higaki M, Sato K, et al. Detection of myeloid precursors (granulocyte/macrophage colony forming units) in the bone marrow adjacent to rheumatoid arthritis joints. *J Rheumatol* 1992;19:1511–1516.
17. Groopman JE, Molina JM, Scadden DT. Hematogenic growth factors: biology and clinical applications. *N Engl J Med* 1989;321:1449–1459.
18. Moore MAS. Clinical implications of positive and negative hematopoietic stem regulators. *Blood* 1991;78:1–19.
19. Kawai M, Hattori H, Yasue K, et al. Development of hemopoietic bone marrow within the ectopic bone induced by bone morphogenetic protein. *Blood Cells* 1994;20:191–199.
20. Palestro CJ, Kim CK, Swyer AJ, Capozzi JD, Solomon RW, Goldsmith SJ. Total hip arthroplasty: periprosthetic ^{111}In labeled leukocyte activity and complementary ^{99m}Tc sulfur colloid imaging in suspected infection. *J Nucl Med* 1990;31:1950–1955.

Patterns of Abnormality on Bone Scans in Acute Childhood Leukemia

Elizabeth J. Bernard, Wayne D. Nicholls, Robert B. Howman-Giles, Stewart J. Kellie and Roger F. Uren
Departments of Nuclear Medicine and Medical Oncology, The New Children's Hospital, Westmead, Australia

Bone scintigraphy is not performed routinely in the diagnostic work-up of children with leukemia; however, the initial diagnosis of childhood leukemia is often difficult to make and may be delayed. Patients may present with fever and skeletal symptoms and, in such cases, bone scintigraphy may be requested in the early search for a diagnosis. Recognition of the potential scintigraphic abnormalities that result from leukemic infiltration of bone and bone marrow will often facilitate an early diagnosis of leukemia. Bone scans also play a role in detecting osteomyelitis in the immunosuppressed leukemic child with fever and bone pain. This article presents four patients illustrating the salient features of bone scintigraphy in these clinical settings.

Key Words: acute lymphoblastic leukemia; bone scintigraphy

J Nucl Med 1998; 39:1983–1986

Leukemia is the most common childhood malignancy and accounts for 30%–40% of all malignancies. Acute lymphoblastic leukemia (ALL) is the most common form and accounts for 85% of cases. The first clinical indication of leukemia may be musculoskeletal symptoms, and patients may be referred for bone scintigraphy before the diagnosis has been made. Several patterns of abnormality on bone scintigraphy may point toward the diagnosis, and an understanding of the potential scintigraphic abnormalities is essential because the changes on bone scans, although not specific, may be the first indication of the possibility of the underlying leukemic process. Patients with a known diagnosis of leukemia may undergo bone scintigraphy to elucidate the cause of bone pain, and, in those with sepsis, a bone scan may be performed to exclude osteomyelitis. This article provides a description of four patients that illustrate the spectrum of potential abnormalities found in leukemic patients at presentation and as complications of the disease process and its medical management.

Received Nov. 6, 1997; revision accepted Mar. 2, 1998.
For correspondence or reprints contact: Elizabeth Bernard, MD, Department of Nuclear Medicine, Royal North Shore Hospital, Pacific Highway, St. Leonards NSW 2065, Australia.

CASE REPORT

Patient 1

A 5-yr-old girl presented with a 2-day history of fever and right leg pain. On examination, she was distressed and had a fever of 39.5°C. She was reluctant to move her right knee and had tenderness over her upper right tibia. Hepatosplenomegaly was noted. Bone scintigraphy was performed to exclude acute osteomyelitis. The scan showed diffuse hyperemia of the metaphyseal regions of the distal femora and proximal tibiae bilaterally. The delayed scan showed a diffuse increase in osteoblastic activity in these areas with loss of the normal metaphyseal/epiphyseal differentiation (Fig. 1A). Figure 1B shows the normal scan appearance for this age for comparison. An infiltrative process, such as leukemia or neuroblastoma, was considered the most likely diagnosis on the bone scan. Bone marrow examination was suggested. The initial blood film was normal. The bone marrow aspirate and trephine revealed ALL. Leukemic lymphoblasts appeared in her blood film several days later. Chemotherapy was begun, and the fevers and leg pain settled quickly. The patient remained well and was in clinical remission 9 mo later.

Patient 2

A 3-yr-old boy presented with fever and a 2-day history of pain in his left shoulder. On examination, he was febrile and had pain on passive movement of his left shoulder. His skin was pale with widespread petechiae and bruises. The blood film and bone marrow examination confirmed the diagnosis of ALL, and chemotherapy was initiated. Because of the focal nature of his shoulder pain, bone scintigraphy was performed to exclude osteomyelitis. The blood-pool phase showed a mild increase in blood flow to the proximal left humerus and the metaphyseal regions surrounding the knees bilaterally. The delayed scan (Fig. 2A) showed increased osteoblastic activity in the metaphyseal region of the proximal left humerus and diffusely increased uptake in the metaphyses of the