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Patterns of Abnormality on Bone Scans in Acute Childhood Leukemia

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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

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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.

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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

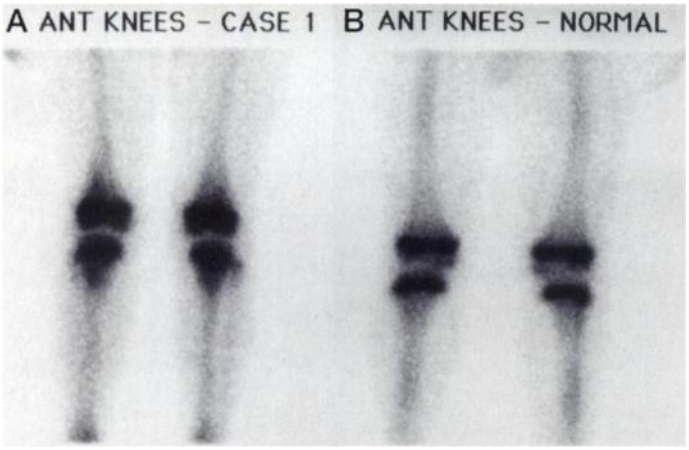

FIGURE 1. (A) Anterior delayed images of knees in 5-yr-old girl show increased tracer uptake in metaphyseal regions of distal femora and proximal tibae. (B) Normal appearance at this age of knees on bone scan, for comparison.

distal femora and proximal tibae. A gallium scan also was performed to determine other sites of infection and revealed abnormal uptake in the proximal left humerus and diffusely throughout the left glenohumeral joint (Fig. 2B) and minimal abnormal uptake in the metaphyseal regions of the lower limbs. Although leukemic infiltration alone could account for the changes in the proximal left humerus on the bone scan, the focal nature of the uptake and the discordance of gallium uptake in this region, as opposed to the other regions of leukemic infiltration evident on the bone scan of the lower limbs, was highly suggestive of superimposed osteomyelitis and septic arthritis of the left shoulder joint. The patient was, therefore, given 6 wk of broad-spectrum antibiotics in addition to chemotherapy. Osteomyelitis recurred after the withdrawal of antibiotic treatment and was demonstrated on a repeat gallium scan with abnormal accumulation in the proximal left humerus. At this time, the leukemic process was known to be well under control, as assessed by bone marrow aspirate and trephine. The patient remained in clinical remission 21 mo after diagnosis.

Patient 3

A 2-yr-old girl presented with 4 wk of intermittent fevers and lethargy, as well as a 1-wk history of inability to walk and reluctance to move her right leg. On examination, she was irritable, febrile and unable to extend her right hip. Initial investigations revealed an erythrocyte sedimentation rate of 82, and the provisional diagnosis was septic arthritis. A right-hip arthrotomy was performed. A moderate amount of sterile seropurulent fluid was drained from the joint, and intravenous antibiotics were given. A review of her blood film noted the presence of leukemic lymphoblasts. Bone scintigraphy (Fig. 3) was performed and showed increased blood flow to the metaphyseal regions of the distal left femur and proximal right femur and reduced blood flow to the head of the right femur. The delayed scan showed absent tracer uptake in the head of the right femur and increased uptake in the adjacent growth plate, the metaphyseal region of the proximal right femur and the distal metaphyseal regions of both femora. The findings indicated an infiltrative process and avascularity of the right femoral head. The scan features were suggestive of leukemic infiltration of bone and bone marrow and were not typical of inflammatory arthritis. The latter was unlikely because there was relatively increased uptake in the proximal right femoral growth plate that would be expected to show reduced uptake in the presence of a significant hip joint effusion, such as may be present in inflammatory arthritis, because the growth plate and the femoral head are intraarticular. Therapy for lymphoblastic leukemia began, and the patient remained in clinical remission, 3 mo after diagnosis, with no residual mobility problems.

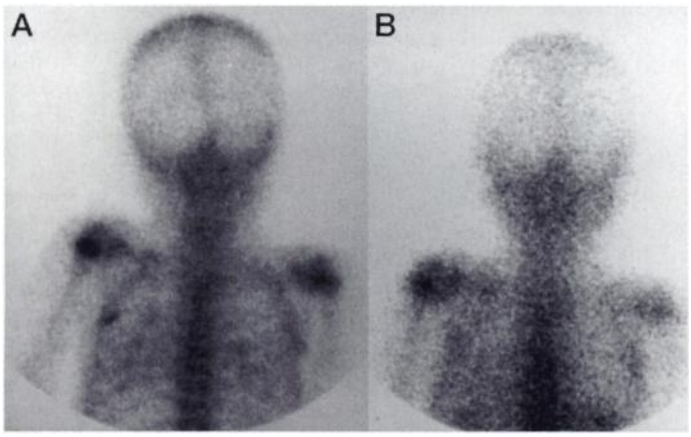

FIGURE 2. (A) Delayed bone scan of posterior thorax in 3-yr-old boy shows increased uptake in proximal left humerus. (B) Gallium scan of posterior thorax shows increased uptake in proximal left humerus and left glenohumeral joint.

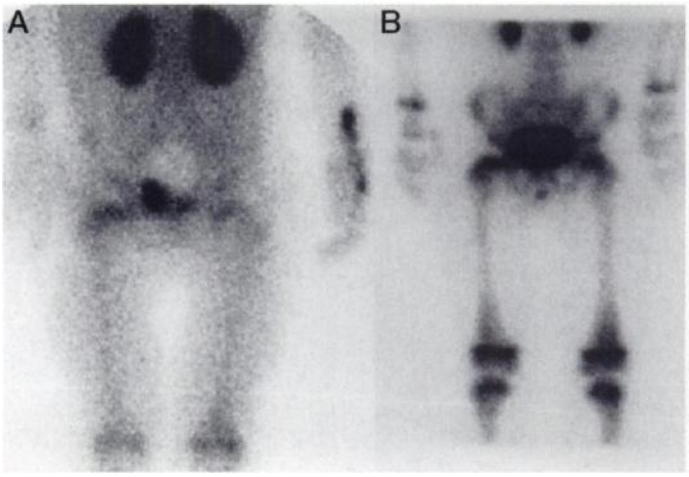

FIGURE 3. (A) Anterior blood-pool image of pelvis and femora in 2-yr-old girl shows reduced blood-pool activity in right femoral head and increased blood-pool activity in proximal right femur and distal left femur. (B) Delayed bone scan of anterior pelvis and femora shows absent tracer accumulation in right femoral head and increased tracer uptake in adjacent growth plate, proximal right femur and metaphyseal regions of distal femora.

Patient 4

A 7-yr-old Caucasian boy presented with 3 wk of lower back pain and right-sided sciatica after a fall. On examination, he was febrile, and the lower back was tender and had moderate hepatosplenomegaly. On investigation, ALL was diagnosed. A bone scan performed to exclude concomitant osteomyelitis showed a mild irregularity of uptake in the shafts of the tibiae and femora and increased uptake in the metaphyseal regions of the distal femora indicative of bone infiltration (Fig. 4A). The appearance of the lumbar spine on the bone scan was normal at that time (Fig. 4B). There was no evidence of focal pathology to suggest concomitant osteomyelitis or trauma. The patient was treated with chemotherapy and 12 mo after diagnosis, during a course of consolidation therapy, acute back pain developed. A bone scan was performed that showed multiple areas of reduced and increased uptake throughout the lumbar spine (Fig. 4D), as well as focal linear uptake in the fifth lumbar vertebral body. Increased uptake was also seen in the distal metaphysis of the left femur (Fig. 4C). MRI of the spine (Fig. 5), performed on the same day as the bone scan, showed loss of height of the fifth lumbar vertebral body. Other

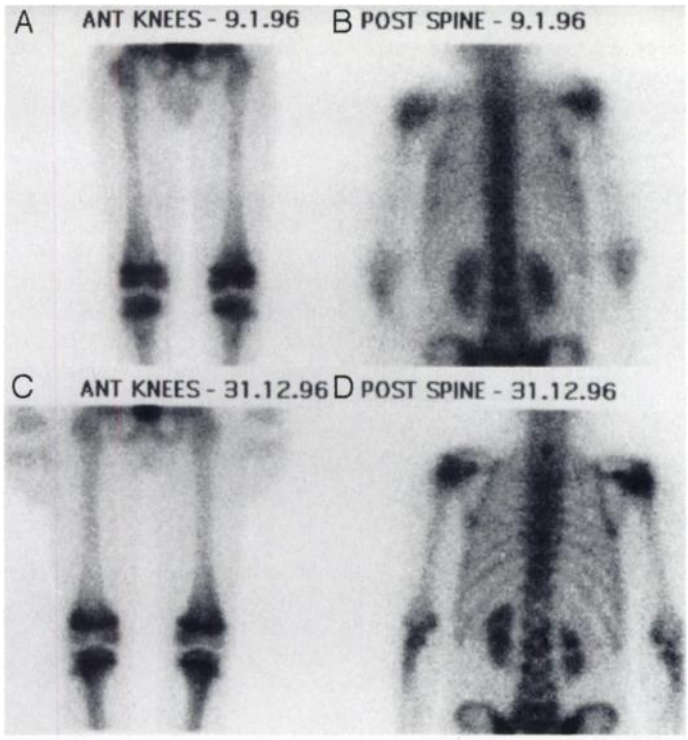

FIGURE 4. (A) Delayed bone scan of knees in 7-yr-old boy shows increased uptake in metaphyseal regions of distal femora and mild irregularity of uptake in femoral shafts. (B) Posterior image of lumbar spine and pelvis at presentation is normal. (C) Delayed bone scan of knees, at time of relapse, shows increased uptake in distal left femoral metaphysis. (D) Posterior image of lumbar spine and pelvis, at relapse, shows foci of increased and decreased tracer accumulation in lumbar spine and linear uptake in L5.

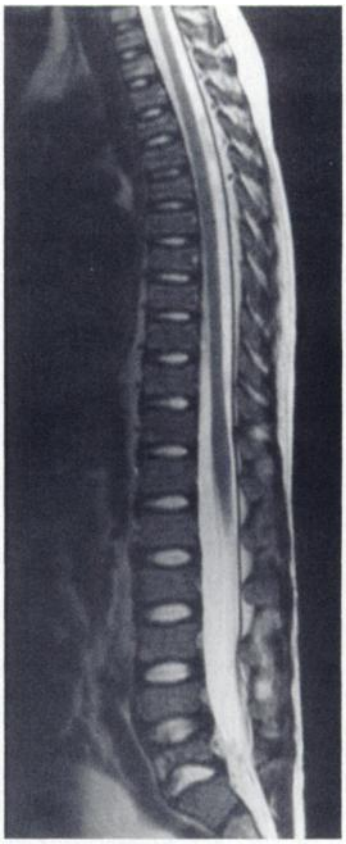

FIGURE 5. MR image of spine in 7-yr-old boy shows loss of height of fifth lumbar vertebral body.

MRI appearances of the lumbar spine were normal. Recurrent leukemia was considered highly likely and, although the peripheral blood film was normal, bone marrow aspirate confirmed the diagnosis of relapse. Second-line chemotherapy was begun, and the patient remained in second clinical remission 3 mo later with no bony symptoms.

DISCUSSION

Musculoskeletal symptoms are present in up to one third of patients at the time of presentation with ALL (*1*). Bone scintigraphy may, therefore, be requested to elucidate the cause of bone pain in a child in whom the diagnosis is not yet known, as well as in patients with known ALL who are considered septic and in whom complicating osteomyelitis should be excluded. Scintigraphic changes are present in 75% of patients with ALL at the time of diagnosis and are due to bone infiltration, which is usually symmetrical and results in diffuse reactivity in cortical bone, most commonly in the metaphyseal regions of the lower limbs. Diffuse involvement of long and flat bones can also occur, and, in blast crisis, the entire bone scan may show increased uptake with accentuation of the ends of the long bones. Less commonly, focal bone abnormalities occur, reflecting focal infiltration of cortical bone by leukemia. In addition, focal infiltration of bone can cause photopenic areas as a result of vascular compromise with avascular necrosis or osteonecrosis (Fig. 4). Therefore, abnormalities can be both focal or diffuse, and both increased or decreased tracer uptake can be seen. An understanding of the potential appearances on bone scintigraphy is important so that the correct diagnosis is considered on the bone scan and the correct diagnostic procedures, examination of the blood film, bone marrow aspirate and trephine, are expediently performed.

The patients described in this article illustrate the spectrum of potential scintigraphic abnormalities that can occur in ALL. The first patient illustrates the appearance of symmetrically increased blood flow and osteoblastic activity in the metaphyseal regions surrounding the knees. Clausen et al. (*2*) studied a group of 24 patients with ALL at presentation, 19 of whom had abnormal bone scans at that time. All patients who had scintigraphic abnormalities had increased uptake in the bones of the lower extremities adjacent to joints, most commonly the knees. In addition, two-thirds of these patients had focal abnormalities at other sites. Pain and radiographic abnormalities have been previously described to occur most commonly near the knees (*3*). Radiographic changes are also common in children with ALL but do not always correlate with the sites of abnormal bone metabolic activity demonstrated on bone scans (*2*). The radiological abnormalities described include radiolucent metaphyseal bands, periosteal reactions, osteolysis, osteosclerosis and, less commonly, generalized osteoporosis and vertebral compression fractures (*4*). It has been proposed that ALL results in abnormal bone metabolism and bone infiltration that can result in structural bone pathology demonstrable radiographically; however, once established, the structural abnormality may remain without metabolic activity (*2*).

The second patient illustrates the frequent clinical dilemma of sepsis complicating the presentation of ALL. This patient had severe, localized bone pain, and bone scintigraphy was used to distinguish local leukemic infiltration from concomitant osteomyelitis. The bone scan illustrates another configuration of abnormalities, both diffuse metaphyseal abnormalities and focal bone uptake, in which leukemia or metastatic malignancy should be considered. The gallium scan in this patient showed discordant uptake, with more intense uptake at the site of the focal bone scan abnormality than in the sites of known bone infiltration in the metaphyses of the long bones. There is little in the literature regarding the usefulness of gallium scintigraphy in this setting. Gallium uptake has been reported in leukemic

masses and, therefore, is theoretically unhelpful (*5*). In this patient, however, gallium scintigraphy correctly diagnosed the coexistence of osteomyelitis by its discordance with the bone scan at known sites of leukemic infiltration. We would suggest the use of gallium scintigraphy or labeled white blood cells in this clinical setting.

The third and fourth patients illustrate the fact that leukemic infiltration can result in photopenic areas on bone scintigraphy. This is due to either compromise to the vascular supply to bone or to bone necrosis caused by the pressure effect from leukemic infiltration. The fourth patient had begun consolidation therapy including high doses of dexamethasone, which has reportedly been associated with avascular necrosis (*6*). The presence of focally increased uptake in the lumbar spine, metaphyseal abnormality in the femur and vertebral compression fracture, however, correctly indicated disease relapse. Photopenia on bone scintigraphy has been previously reported and may occur at presentation or at the time of relapse (*7*). Photopenia also has been described in relation to methotrexate therapy in the absence of leukemic infiltration (*8*). Leukemia is a rare cause of a focal photopenic lesion on bone scintigraphy but should be considered in the differential diagnosis, especially in the presence of concomitant abnormal uptake in the metaphyseal regions of the lower limbs and other focal bone scan abnormalities. A vertebral compression fracture developed at the time of disease relapse in the fourth patient. Alterations in mineral homeostasis and bone mass have been reported in patients with ALL both at the time of diagnosis and after treatment involving prednisone and methotrexate. Halton et al. (*1*) described defective mineralization as the mechanism for decreased bone mass. Therefore, patients with ALL can develop stress and compression fractures at the time of presentation or after treatment, which may be evident on scintigraphy. Alternatively, this complication may be due to a destructive process by leukemic cells. A review by Ribeiro et al. (*4*) described vertebral compression fractures in 1.6% of patients at the time of diagnosis. Vertebral compression fractures should be considered in the spectrum of potential scintigraphic abnormalities in patients with ALL.

In performing pediatric bone scans, special attention should be paid to correct technique to acquire precisely symmetrical images with the limbs as straight as possible so that the appearance of the epiphyseal–metaphyseal junction can be properly assessed. Lack of attention to technical detail may lead to diagnostic inaccuracy, because the growth plates may appear blurred if not imaged perpendicular to the collimator. There is usually a clear differentiation between the intense, symmetrical horizontal uptake in the growth plates and low-level uptake in the adjacent metaphyses. When there is a loss of distinction of the epiphyseal–metaphyseal junction and abnormal uptake in the metaphyseal regions, pathological processes such as leukemia, lymphoma, metastatic neuroblastoma or osteomyelitis should be considered, because all of these processes can cause symmetrical metaphyseal abnormalities. Radiographic examination of positive scintigraphic sites should be performed and correlated with scintigraphy.

CONCLUSION

Knowledge of scintigraphic changes that occur in the setting of acute childhood leukemia and its treatment will expedite the early diagnosis of leukemia at presentation and the diagnosis of complications during therapy.

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Reverse Ventilation–Perfusion Mismatch in Lung Cancer Suggests Intrapulmonary Functional Shunting

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We report on a patient with squamous cell cancer of the left lung who was first considered ineligible for surgery because of severe hypoxemia. A ventilation–perfusion scan showed "reverse" ventilation–perfusion mismatch, with 20% of the total lung perfusion going to the left lung, which showed no ventilation with radioactive aerosols. This pattern suggested that the hypoxemia was due to intrapulmonary functional shunting and could therefore be improved by surgical resection of the tumor. Balloon occlusion of the left pulmonary artery resulted in an immediate rise in PaO_2, indicating a right-to-left intrapulmonary shunt. After left pneumonectomy, PaO_2 levels were normal. This patient provides an example of dysregulation of the pulmonary hypoxic vasoconstriction response in a non-small cell lung cancer. Lung cancer patients with severe hypoxemia should undergo ventilation–perfusion scanning to look for reverse ventilation–perfusion mismatch suggestive of intrapulmonary functional shunting.

Key Words: bronchial cancer; hypoxemia; intrapulmonary functional shunting; ventilation–perfusion lung scan

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