
^{99m}Tc -MDP Scintigraphic Findings in Children with Leukemia: Value of Early and Delayed Whole-Body Imaging

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The purpose of this study was to reveal the bone scan abnormalities in children with leukemia and to show the value of whole-body scanning in early and delayed phases. **Methods:** From a database of all patients with a diagnosis of leukemia from January 1990 to April 2000, 12 children (9 male, 3 female; mean age, 8.0 y; age range, 4.7–13.2 y) were identified for whom the diagnosis of leukemia was suggested on the basis of bone scans obtained as part of the initial work-up for unexplained skeletal pain. Early and delayed whole-body bone scans and radiographs were reviewed retrospectively. Areas of abnormal uptake on early and delayed phases were categorized into locations: metaphysis–diaphysis–epiphysis (MDE), pelvis, ribs, spine, and others. MDE lesions included abnormalities in the metaphysis extending into the diaphysis for some length: metaphysis/diaphysis, metaphysis only, diaphysis only, epiphysis only, and the entire bone. Pelvic and spine lesions were further characterized as focal or diffuse. **Results:** Ten patients had lesions in 2 or more locations on both phases. Two patients had multiple lesions on the early scans but only rib lesions on the delayed scans. Lesions correlated with symptomatic sites in 8 patients on the delayed scans and in 11 patients on the early scans. The most common sites of abnormalities on the delayed scans were metaphyseal/diaphyseal, pelvis (focal), and ribs. The most common locations of lesions on the early scans were metaphyseal/diaphyseal, pelvis (diffuse or focal), and spine. More metaphyseal/diaphyseal lesions were seen on the early scans than on the delayed scans. Diffuse involvement of the pelvis and spine was seen only on the early phase. However, rib lesions were seen more frequently on the delayed scan. **Conclusion:** Early whole-body imaging in conjunction with delayed whole-body scanning may enhance the diagnostic accuracy of bone scanning in the evaluation of children with skeletal pain of obscure etiology, such as that associated with leukemia.

Key Words: bone scintigraphy; whole-body imaging; leukemia

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Skeletal pain in children can have multiple etiologies, including trauma, infection, and malignancy. Bone scintigraphy has been shown to be useful in the diagnostic work-up of unexplained bone pain (1–3). Leukemia, the most common malignancy in children, will usually manifest itself with characteristic clinical and laboratory findings, leading to the correct diagnosis. Occasionally, however, the primary presenting feature in leukemia is persistent, often multifocal, musculoskeletal pain. In an attempt to diagnose the etiology of the pain, children who present in this fashion may undergo bone scanning. We reviewed the whole-body bone scans of 12 children who presented with unexplained bone pain and who were later proven to have leukemia. The abnormal findings of leukemia on ^{99m}Tc -methylene diphosphonate (MDP) scintigraphy are presented, with emphasis on whole-body imaging in the delayed and early phases.

MATERIALS AND METHODS

From the medical records at Children's National Medical Center from January 1990 to April 2000, 263 patients with the diagnosis of leukemia were found. Review of their radiology records identified 12 patients (9 male, 3 female; mean age, 8.0 y; age range, 4.7–13.2 y) who had undergone skeletal scintigraphy as part of the initial diagnostic work-up for persistent unexplained skeletal pain (Table 1). Ten of the 12 patients had multifocal bone pain. Other symptoms and signs included fatigue, fever, anemia, weight loss, and elevated erythrocyte sedimentation rate. Ten of the 12 patients had had radiography of certain symptomatic areas; 8 patients had normal findings, 1 showed a permeative pattern (in retrospect) in the radius and ulna, and 1 had a periosteal reaction in both ulnae.

All bone scans were obtained on a dual-detector gamma camera with acquisition of simultaneous anterior and posterior whole-body images (routine for all bone scans since 1990). The dose used was 9.3 MBq/kg (250 $\mu\text{Ci}/\text{kg}$), with a minimum dose of 110 MBq (3 mCi) and a maximum dose of 750 MBq (20 mCi) ^{99m}Tc -MDP. Flow imaging of the most symptomatic area was performed in 5 of the 12 patients, whereas early and delayed whole-body images were obtained on all patients. Early whole-body images were obtained at a scanning rate of 40 cm/min, with imaging completed within 5 min of the injection. Delayed whole-body imaging was done 2–3 h after injection at a scanning rate of 8 cm/min.

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TABLE 1
Patient Data

Patient no.	Age (y)	Sex	Clinical history	Radiographs	Bone scans	
					Early	Delayed
1	7.4	F	Bilat hip pain	Normal	m/d: bilat dist femur and bilat prox tibia, unilat prox humerus, unilat prox fibula; pelvis (d); spine (d); ribs	Ribs
2	4.7	M	Bilat leg and knee pain; fever; elevated ESR; anemia	None obtained	Pelvis (f); spine (d)	Pelvis (f); ribs
3	6.3	M	Bilat ankle and forearm pain; fatigue	Permeative radius/ulna (in retrospect)	m/d: left dist radius, bilat dist fibula, right forearm	m/d: left dist radius, bilat dist fibula; right ulna diffusely
4	8.1	M	Bilat thigh and right shoulder pain	Normal	m/d: bilat dist femur and bilat prox tibia, unilat prox humerus	m/d: bilat dist femur and bilat prox tibia; ribs
5	12.9	M	Bilat knee pain; anemia; weight loss	Normal	m/d: bilat dist femur and bilat prox tibia, bilat prox humeri, unilat prox fibula; scapula	m/d: bilat dist femur and bilat prox tibia, bilat prox humeri, unilat prox fibula; scapula; ribs; skull
6	7.4	M	Left hip and leg pain; fever	Normal	m/d: bilat dist femur and bilat prox tibia; spine (d); pelvis (d); ribs	Ribs
7	7.2	F	Right hip and thigh pain; anemia; elevated ESR	Normal	Unilat femoral diaphysis; pelvis (f)	Unilat femoral diaphysis; pelvis (f)
8	11.3	F	Back pain; fever	Normal	m/d: bilat dist femur and bilat prox tibia, unilat dist ulna; unilat dist radius diaphysis, single rib; pelvis (d), spine (d)	m/d: unilat dist ulna, unilat dist radius diaphysis; single rib; skull
9	4.8	M	Right hip pain; fever	Normal	Unilat dist femoral metaphysis; pelvis (f)	Unilat dist femoral metaphysis; pelvis (f)
10	7.3	M	Right hip and leg pain; fever	Normal	m/d: unilat prox tibia; bilat dist femoral epiphysis; pelvis (d); scapula	Pelvis (f); scapula; sternum
11	13.2	M	Bilat hip, elbow, and knee pain; fever	None obtained	m/d: bilat dist femur and bilat prox tibia, bilat prox humeri, bilat prox fibula, bilat dist tibia; pelvis (f); bilat clavicles	m/d: bilat dist femur and bilat prox tibia, bilat prox humeri, bilat prox fibula, bilat dist tibia; pelvis (f), bilat clavicles; skull
12	5	M	Bilat hand and foot pain	Periosteal reaction bilat ulna	m/d: bilat dist femur and bilat prox tibia, unilat dist radius; unilat ulnar diaphysis; unilat fibular epiphysis	m/d: unilat dist radius; diaphyses of bilat ulnae, femurs, tibiae, fibulae ; unilat fibular epiphysis; pelvis (f)

bilat = bilateral; m/d = metaphysis/diaphysis; dist = distal; prox = proximal; unilat = unilateral; d = diffuse; ESR = erythrocyte sedimentation rate; f = focal.

Boldface type indicates areas seen only on 1 phase (early or delayed).

The bone scans were reviewed retrospectively. Areas of abnormal uptake were documented by phase and location in the following categories: metaphysis–diaphysis–epiphysis (MDE) (including lesions extending from metaphysis to diaphysis [metaphyseal/diaphyseal], lesions in metaphysis only, diaphysis only, epiphysis only, or entire bone), pelvis, ribs, spine, and others. The spine and pelvic lesions were further characterized as focal or diffuse. Because flow imaging had been performed on less than half of the patients, this phase was omitted from the review.

RESULTS

General

All patients except 2 (patients 1 and 6) had lesions in 2 or more locations on the delayed scans (Table 1). These 2 patients had lesions only in the ribs, although multiple ribs were involved in each patient. The most common sites of lesions on the delayed phase were the MDE (8/12 patients), the pelvis (focal) (6/12 patients), and the ribs (6/12 patients)

TABLE 2
Distribution of Lesions by Location and Phase
for All Patients ($n = 12$)

Location	Phase	
	Early	Delayed
MDE	11	8
m/d	9	6
Pelvis	8 (4 focal, 4 diffuse)	6 (focal)
Ribs	3	6
Spine	4 (diffuse)	0
Other (skull, scapula, clavicle, sternum)	3	4

m/d = metaphysis/diaphysis.

(Table 2). Nearly all lesions showed increased uptake, with heterogeneous lesions seen in some ribs. However, no large photopenic defects were seen. The locations of lesions correlated with the sites of pain in 8 of the 12 patients. Additional lesions were seen in asymptomatic sites in 10 patients.

All patients had lesions in 2 or more locations on the early-phase scans (Table 1). The most common sites of lesions were the MDE (11/12), the pelvis (8/12), and the spine (4/12) (Table 2). The sites of abnormalities corre-

sponded with areas of pain in 11 of the 12 patients. Additional lesions were seen in asymptomatic areas in 9 patients (Fig. 1). The final diagnosis for all patients was acute lymphocytic leukemia.

Specific

MDE Lesions. The predominant pattern of involvement was a metaphyseal lesion extending to the diaphysis up to approximately one third of the shaft length (metaphyseal/diaphyseal). These metaphyseal/diaphyseal lesions were seen in 6 of 8 patients with MDE lesions on the delayed scans and in 9 of 11 patients with MDE lesions on the early scans (including the 6 patients with abnormal delayed scans). In addition, this metaphyseal/diaphyseal involvement was bilateral in 4 of 6 patients on the delayed scans and in 8 of 9 patients on the early images (including the 4 patients with bilateral lesions on the delayed scans). Lesions involving only the metaphysis or only the diaphysis were present in 3 patients (patients 7–9) on the early and delayed scans. Two additional patients had epiphyseal lesions as well as metaphyseal/diaphyseal abnormalities. In 1 patient (patient 12), the abnormality was present on the early and delayed phases. In the other patient (patient 10), the uptake was seen only on the early images. In 1 other patient, diffuse involvement of the entire bone was present on both phases (patient 3).

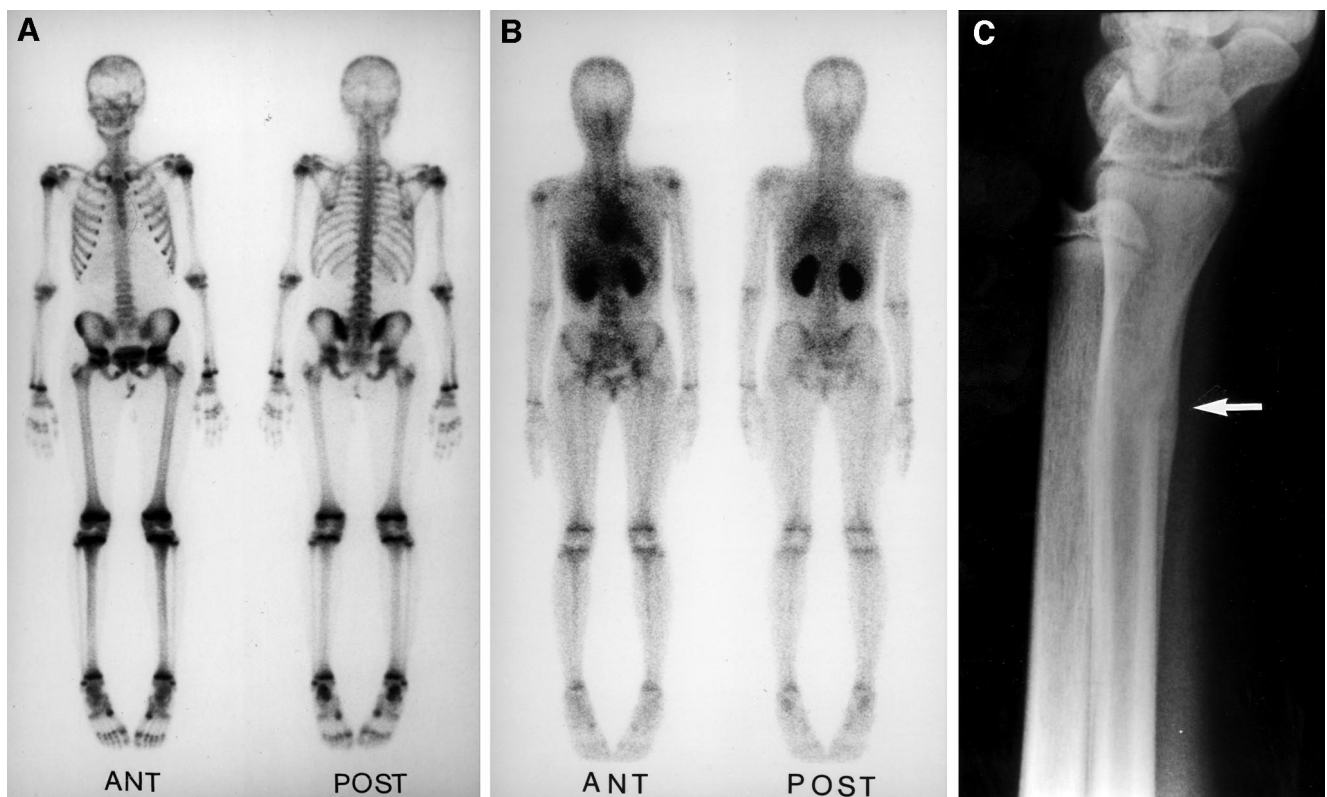


FIGURE 1. Patient 8 (11.3-y-old girl) who presented with fever and back pain. (A) Early whole-body images show multifocal areas of abnormal uptake, including metaphysis/diaphysis of bilateral distal femurs, bilateral proximal tibiae, and right distal ulna; left distal radius diaphysis, right first rib, pelvis, and spine show diffuse uptake. (B) Delayed whole-body images reveal uptake in right first rib, skull, right distal ulnar metaphysis/diaphysis, and left distal radius diaphysis, shown to be healing fracture on radiograph, lateral view (arrow) (C). Spine, site of patient's pain, is normal. SPECT imaging of spine was also normal (not shown).

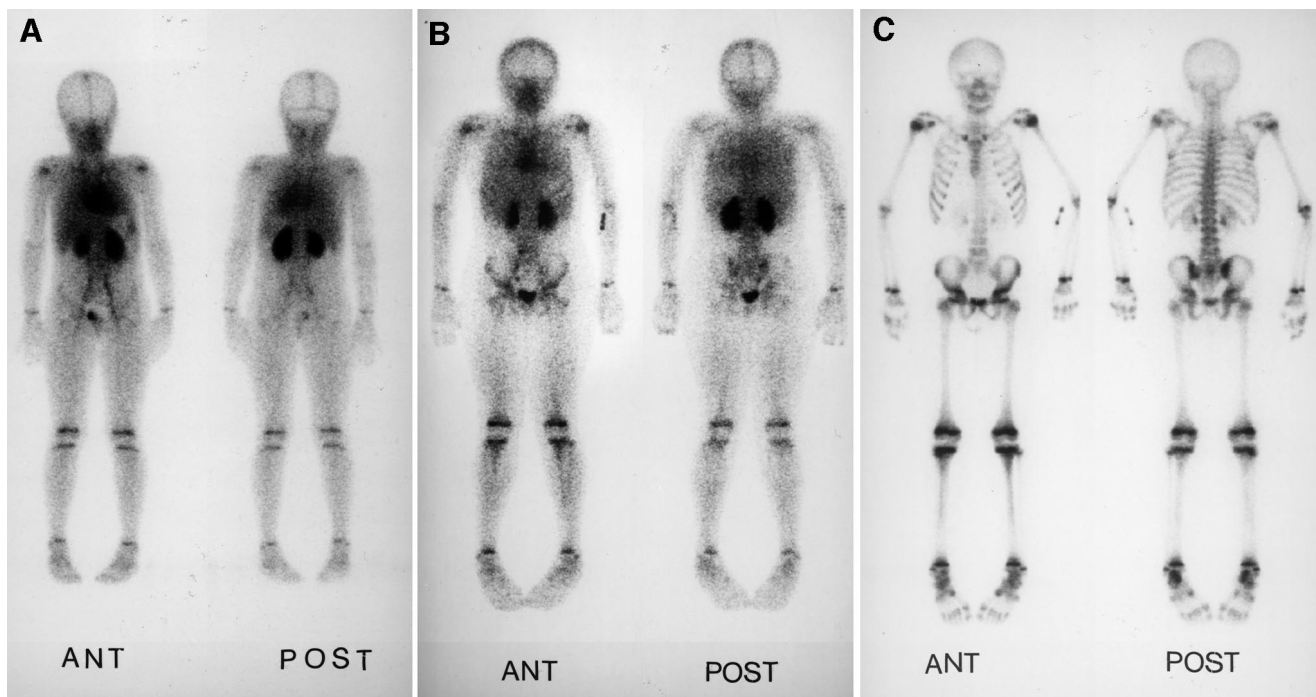


FIGURE 2. Patient 1 (7.4-y-old girl) who presented with bilateral hip pain. (A) Early whole-body images show intense diffuse abnormal uptake in pelvis, thoracic and lumbar spine, bilateral anterior ribs, and metaphysis/diaphysis of bilateral distal femurs, bilateral proximal tibiae, left proximal fibula, and left proximal humerus. Note symmetric involvement of knees. (B) Normal early whole-body images show minimal tracer uptake in skeleton. Note minimal tracer accumulation in bladder attributed to early phase of scanning (A and B). (C) Delayed whole-body images reveal heterogeneous abnormal uptake in bilateral ribs. Remainder of bone scan is normal, including hips, where patient was symptomatic.

Pelvis. Focal pelvic lesions were seen in 6 patients on the delayed images. Four of these had corresponding foci of abnormality in the pelvis on the early scans, whereas no abnormality was seen on the early scans in the other 2 patients. Diffuse abnormal uptake in the pelvis was seen only on the early images in 4 other patients (Table 2).

Ribs. Rib lesions were seen much more frequently (6 patients) on the delayed scans compared with those seen (3 patients) on the early scans. Rib lesions almost always involved multiple ribs, except in 1 patient (patient 8).

Spine. Lesions in the spine were diffuse in appearance, were present in 4 patients, and, similar to the diffuse pelvic lesions, were seen only on the early images (Fig. 2). Symptomatic painful sites correlated with abnormalities on bone scans in 3 additional patients on the early phase compared with the delayed phase. These 3 patients had hip pain (patients 1 and 6) and spinal pain (patient 8). The corresponding abnormalities on the early scans were diffuse abnormal uptake in the pelvis and spine, seen only on the early phase.

DISCUSSION

Children with leukemia who present with primarily musculoskeletal symptoms comprise a small but important group. In 2 reported series, a significant number of patients with a presumed diagnosis of arthritis were later proven to have leukemia: 10 of 13 children in the series of Schaller (4)

and 13 of 29 children in the series of Cabral and Tucker (5). A smaller subset of this group may undergo skeletal scintigraphy to help elucidate the etiology of their pain. Patients with leukemia (both children and adults) have been shown to have abnormalities, often multifocal, on bone scintigraphy (6–11). All patients in our study had multiple lesions on the delayed scans. Lesions were also present in asymptomatic sites. This finding emphasizes the importance of whole-body scanning. Limiting the imaging to the symptomatic areas would omit detection of other abnormal sites. Thus, multifocal abnormalities emerge by whole-body scanning, even in asymptomatic sites.

The most common sites of lesions seen on the delayed scans were the MDE, particularly the metaphysis/diaphysis, pelvis, and ribs. In the metaphyseal/diaphyseal lesions, the lower limbs were involved more frequently compared with the upper extremities. This predilection for metaphyseal/diaphyseal involvement, especially in the lower extremities, was also seen in the series of Clausen et al. (6) and Bernard et al. (11). Rib lesions were seen in half of our patients. Rib involvement was frequent in adults in the series of Hoshi et al. (9). Almost all lesions in our series showed increased uptake, except for scattered rib lesions that were heterogeneous. Large photopenic defects have been reported as the primary bone scan lesions of leukemia on presentation (12,13). These were not present in any of our patients.

Demonstration of lesions on the early scans of all patients was the most interesting finding in this study. Ginsberg and Swayne (8) and Bernard et al. (11) also described leukemic lesions on the early images; however, to our knowledge whole-body scanning was not done. In most instances in our patient series, uptake on the early scans, when present, paralleled uptake on the delayed scans, especially in the metaphyseal/diaphyseal lesions. In 3 patients, metaphyseal/diaphyseal abnormalities were seen only on the early phase (patients 1, 6, and 10). In 3 additional patients (patients 4, 8, and 12), more lesions were seen in the metaphysis/diaphysis on the early phase compared with the delayed phase.

Diffuse abnormal uptake in the pelvis and spine seen only on the early scans was a unique finding in this study. This diffuse involvement was strikingly intense on the early phase and strikingly normal on the delayed phase. To our knowledge, this finding has not been reported previously. Because the pelvis and spine are sites with a high concentration of hematopoietic marrow, this diffuse uptake on the early phase may represent concentration of the tracer in bone marrow infiltrated by leukemia. This may also explain the uptake in the metaphyseal/diaphyseal areas. Other malignancies that infiltrate the bone marrow may also behave in this manner, such as neuroblastoma, rhabdomyosarcoma, and lymphoma.

Malignancy is a prime differential consideration for multiple foci of abnormal uptake on delayed bone scans. Multiple abnormalities were present in all of our patients on the delayed images. What then is the usefulness of obtaining early whole-body scans? The presence of abnormal uptake on the early images can facilitate the overall interpretation of the scan. Many lesions seen on the delayed images were also abnormal on the early scans. The presence of concomitant areas of abnormality on the early images can help to confirm questionable findings on the delayed scans. This is especially true with metaphyseal/diaphyseal lesions. Lesions in this location, especially when bilateral and symmetric, can be difficult to interpret on the delayed scans. In addition, uptake in a lesion on early and delayed phases strongly suggests that the lesion is active. Additional lesions, as indicated by diffuse abnormal uptake in the pelvis and spine, may be present on the early scans and not on the delayed images. Finally, metaphyseal/diaphyseal lesions may be more extensive on the early phase compared with the delayed phase. The findings on the early scan together with those on the delayed scan can more firmly lead to appropriate diagnostic evaluation.

Careful attention to timing is important when performing and interpreting the early images. A true reflection of the early phase is probably best when scanning is done immediately after the first minute of flow and completed within the first 5 min of injection. If imaging is delayed, the normal accumulation of MDP in bone can be mistaken for abnormal uptake on the early image. Using a scanning speed of 40 cm/min, an adult patient up to a height of 200 cm can be scanned within 5 min.

Patient 8 (Fig. 1), in particular, illustrates the value of whole-body imaging in both phases and perhaps also the sensitivity of bone scanning in detecting abnormalities in leukemia. This patient presented with a 2-wk history of fever and back pain. The early images showed uptake in the metaphyses/diaphyses of both distal femurs and proximal tibiae, right distal ulna, left distal radius, and 1 rib as well as diffuse uptake in the pelvis and spine. The delayed images showed lesions in the skull, 1 rib (same rib as on early images), right distal ulna, and left distal radius (proven to be a healing fracture). SPECT imaging of the spine was normal. Bone marrow aspiration was performed on the basis of bone scan abnormalities, particularly on the early phase. This showed only 10% blasts in the marrow, which was inconclusive for the diagnosis of leukemia but probably represented a preleukemic state. The patient returned <2 wk later with increasing symptoms of pain. Bone marrow aspiration was repeated and was definitive for the diagnosis of acute lymphocytic leukemia.

The diagnosis of a marrow infiltrative process was suggested prospectively on the basis of the bone scan findings in all patients except patient 9. In this patient with hip pain, only a single focus of abnormality (pelvis) was noted at the time of interpretation of the scan. The distal femoral metaphyseal lesion was seen only in retrospect. The diagnosis of leukemia was suggested on the basis of hip MRI 1 mo later.

CONCLUSION

Leukemia in children may present as multifocal bone pain. Whole-body scanning in the early and delayed phases will often reveal multiple lesions, even in asymptomatic sites. Limiting the imaging to the area(s) of interest on either the early phase or the delayed phase may result in loss of important diagnostic information. Uptake on early scans often parallels the findings on delayed scans, especially in the metaphyseal/diaphyseal regions. Abnormal findings may be more extensive on early scans than on delayed scans. Diffuse uptake in the pelvis and spine, sites of high hematopoietic activity, is seen only on the early phase and may suggest marrow infiltrative disease. Therefore, early whole-body imaging in conjunction with delayed whole-body scanning may enhance the diagnostic accuracy of bone scanning in the evaluation of children with skeletal pain of obscure etiology, such as that caused by leukemia.

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