Multifocal Osteonecrosis Following Chemotherapy and Short-Term Corticosteroid Therapy in a Patient with Small-Cell Bronchogenic Carcinoma

D.N. Jones

Division of Nuclear Medicine, Department of Radiology, Duke University Medical Center, Durham, North Carolina

This report describes the development of multiple-site, biopsy-proven osteonecrosis in a patient with small-cell bronchogenic carcinoma who had received chemotherapy and short-term administration of corticosteroid. Multifocal osteonecrosis has a wide variety of etiologies, but is most often encountered in the clinical setting of corticosteroid administration, connective tissue disorders, transplantation, hemoglobinopathies and dysbarism. In the oncology patient, chemotherapy, corticosteroids and bone marrow transplantation (with associated preparation therapy) have all been implicated as possible causes. There may be a synergistic effect when corticosteroids are used in combination with chemotherapy and radiation treatment. Multiple periarticular abnormalities appearing on serial radionuclide bone scanning of the cancer patient, particularly when symmetric and in a distribution not suggestive of osseous metastatic disease, raise the possibility of multifocal osteonecrosis. Also to be considered in the differential diagnosis are multifocal infection and polysynovitis/arthritis of other etiology. MRI has a high sensitivity and specificity in the diagnosis of osteonecrosis and should be used when this condition is suspected. Early diagnosis of osteonecrosis is important to prevent irreversible bone and joint destruction.

Key Words: osteonecrosis; radionuclide bone scanning; corticosteroids; chemotherapy

J Nucl Med 1994; 35:1347–1350

CASE REPORT

A 53-yr-old male presented with hemoptysis. A chest radiograph demonstrated a left upper lobe mass and infiltrate, and CT of the thorax and abdomen showed hilar and mediastinal lymph node enlargement and multiple liver lesions consistent with metastatic disease. Histological analysis following bronchoscopy confirmed small-cell bronchogenic carcinoma. A CT scan of the brain, bone scan (Fig. 1) and bone marrow biopsy were negative for metastatic disease. Seven cycles of chemotherapy (carboplatinum, etoposide) were administered over the next 6 mo. A repeat bone scan was normal. Ten months following initial diagnosis, the

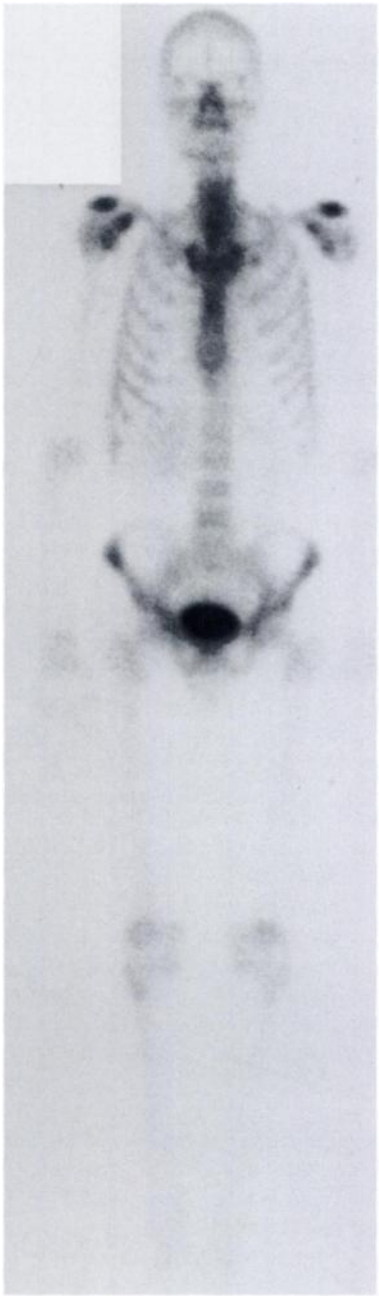

FIGURE 1. Skeletal-phase anterior whole-body scan performed at time of diagnosis shows no abnormality.

Received Dec. 9, 1993; revision accepted March 31, 1994.

For correspondence or reprints contact: D.N. Jones, MD, Division of Nuclear Medicine, Department of Radiology, Box 3949, Duke University Medical Center, Durham, NC 27710.

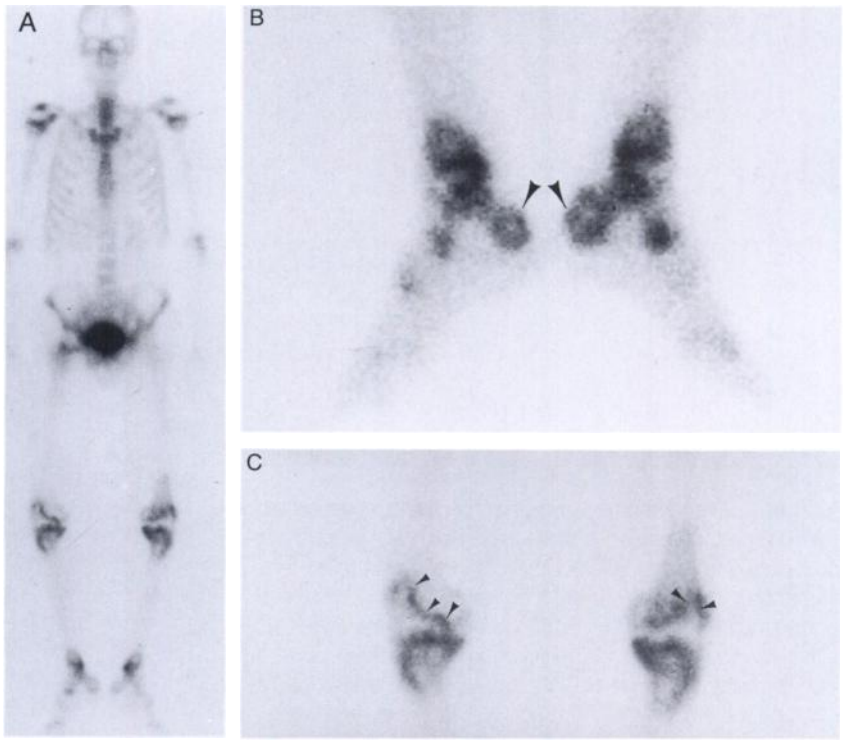

FIGURE 2. (A) Three months after initiation of a 10-day corticosteroid course and an additional three cycles of chemotherapy, imaging demonstrates increased periarticular tracer uptake about both ankle and knee joints and increased uptake in both humeral heads and the neck of the proximal right femur. (B) Medial images of both feet show symmetric increased uptake adjacent to both ankle joints and in the hind and mid feet. Note peripheral circular tracer uptake within the calcanei (arrowheads). (C) Anterior view of both knees demonstrates pronounced serpiginous increased uptake (arrowheads) and diffuse increased uptake in the distal femora and proximal tibiae. The serpiginous uptake correlates with the reactive interface between normal and infarcted bone as demonstrated on MRI (Fig. 3B).

patient presented with signs and symptoms of raised intracranial pressure and a CT brain examination confirmed multiple metastases and signs of cerebral edema. Intravenous dexamethasone (Decadron, Merck, Sharp and Dohme) was administered, initially 10 mg every 6 hr for several days, then tapering over the next 7 days (10-day course—estimated total dexamethasone dose approximately 200–250 mg). Whole-brain irradiation (30 Gy in 10 fractions) was also administered. A repeat bone scan obtained 3 days after initiation of corticosteroid therapy again showed no abnormality. Following three cycles of chemotherapy (cisplatinum, etoposide) over a 3-mo period, the patient reported generalized joint pains involving feet, knees, hips and shoulders, particularly pronounced in the region of the right hip. A bone scan demonstrated increased tracer uptake in the bones of the hind and mid-foot bilaterally, in the epiphysis and metaphysis of the long bones adjacent to the ankle, knee and shoulder joints bilaterally, and in the neck of the proximal right femur (Fig. 2). The distribution of abnormalities was not typical for metastatic bone disease, and multifocal osteonecrosis, polysynovitis/arthritis and infection were considered in the differential diagnosis. MRI of the lower extremities confirmed characteristic findings of extensive osteonecrosis (Fig. 3). A small left-femoral head lesion was not identifiable on bone scan. A right hip-joint effusion was also seen and a linear hypointense zone in a transcervical position, seen on T1 weighted images, suggested the possibility of an undisplaced proximal femoral fracture complicating bone infarction in this region. A right hip joint aspiration yielded cloudy yellow fluid containing some inflammatory cells, but microscopy and cultures were negative for infection. At surgery, an undisplaced fracture was confirmed and treated with screw fixation. An intraoperative bone biopsy revealed bone infarction, without evidence of metastatic disease.

DISCUSSION

Osteonecrosis (avascular necrosis, ischemic necrosis) is defined as the in situ death of a segment of bone. There are two major forms: medullary bone infarction, involving the trabecular architecture and marrow cavity and usually clinically silent; and corticomedullary infarction, which is typically subchondral in site, painful and classically involves the humeral and femoral heads (*1*).

Several pathogenetic mechanisms have been proposed including mechanical vascular interruption (for example, femoral neck fracture), thrombosis and embolism, injury of or external pressure on a vessel wall, and venous occlusion (*1*). Pathologically, medullary infarcts are nonprogressive lesions. When they involve fatty marrow, insoluble soaps are formed by the interaction of released calcium and fat. These abnormalities are usually clinically silent and persist for life. Corticomedullary osteonecrosis, however, is a progressive, often painful lesion most often involving the femoral head, medial femoral condyle and humeral head. Small lesions may be clinically silent but detectable on imaging. Following the death of cortex, bone marrow and medullary bone, repair is initiated first by hyperemia and the formation of reactive granulation tissue at the interface with normal bone. Revascularization of the dead tissue begins a few weeks later by ingrowth of vessels from the surrounding reactive tissue. New bone formation accompanies this process and is laid down on the old framework ("creeping substitution"). The repair process, however, may continue unabated and ultimately lead to loss of bone integrity,

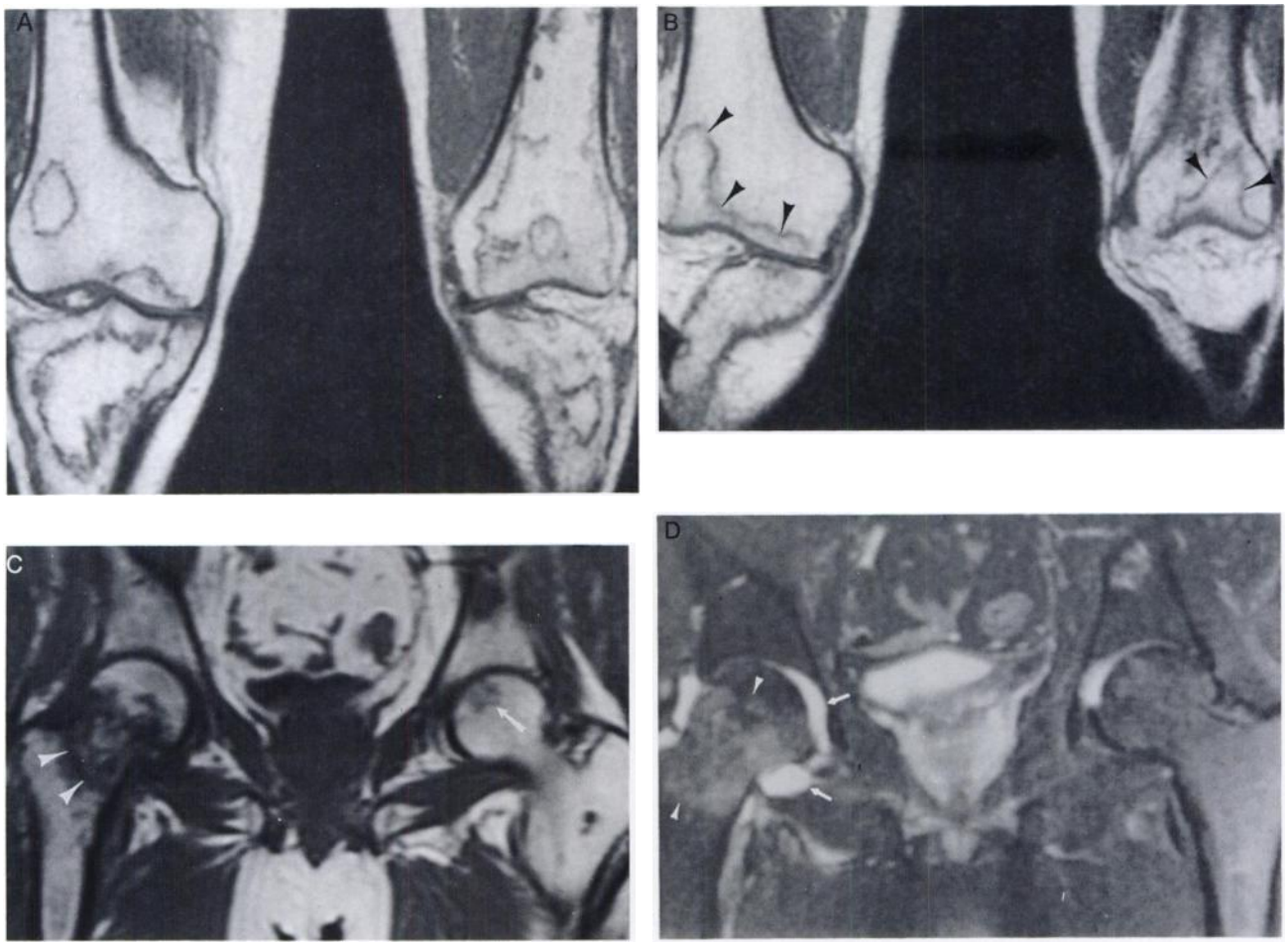

FIGURE 3. (A) Coronal spin-echo T1-weighted (500/15/2) images of the knees demonstrate typical appearances of medullary and corticomedullary infarcts extending to the articular surface. (B) A more anterior coronal MR slice of the knees (same pulse sequence as Fig. 3A) demonstrates the reactive interface between normal and infarcted bone (arrowheads) correlating with the corresponding increased tracer uptake on bone scan (Fig. 2C). (C) Coronal spin-echo T1-weighted (500/10/2) images of the hip joints demonstrate focal infarcts in both proximal femora (arrow indicates small infarct in left femoral head). A curvilinear hypointensity at the base of the neck of the proximal right femur (arrowheads) is suggestive of a pathological fracture through the bone infarct. (D) Coronal fast spin-echo (4000/50/2) image demonstrates a right hip-joint effusion (arrows) and marrow edema involving the neck and head of the proximal right femur (arrowheads).

collapse of subchondral bone support, stress fractures, cartilage degeneration, deformity and secondary osteoarthritis (*1*).

Imaging of osteonecrosis usually involves plain radiographs (which form a basis for staging the disease process), radionuclide bone scanning and MRI. MRI is the most sensitive imaging modality in the detection of osteonecrosis and has a relatively specific appearance (*2–5*). Both bone and bone marrow scanning may be utilized in the radionuclide imaging of osteonecrosis. In the early phases of the disease process, absent perfusion and osseous tracer uptake are seen on bone scan and absent marrow activity is seen on marrow scanning. In the later phases (after approximately 1 mo), return of some peripheral perfusion and osseous activity may be seen on bone scanning, correlating with revascularization and healing (*7*). These later-phase images, however, may be difficult to interpret as a result of increased activity around and within the bone infarct secondary to revascularization and bone healing. SPECT may be a useful adjunct in this particular situation by providing three-dimensional information (*6*).

Osteonecrosis has a large number of etiologies which can form a basis for the classification of this disease. Traumatic, septic and nontraumatic causes of osteonecrosis are recognized in addition to childhood cases of osteonecrosis (e.g., Legg-Calve-Perthes disease) which are often grouped and considered separately (*1*).

Multifocal osteonecrosis is an uncommon entity usually seen in the clinical setting of corticosteroid administration, connective tissue disorders (e.g., rheumatoid arthritis and systemic lupus erythematosus), dysbarism, hemoglobinopathies (e.g., sickle cell disease), arteritis/vasculitis, pancreatitis, Gaucher's disease, pregnancy and alcohol abuse (*1*). Multiple-site osteonecrosis has been reported in two patients with HIV infection, but the role of the latter in bone necrosis is questionable (*8*). Multifocal osteonecrosis is also reported in patients who have undergone renal, cardiac or bone marrow transplantation (*1,9–11*), and in

oncology patients who have received chemotherapy. In oncology patients, however, it is often difficult to isolate a single causative agent because the underlying disease process, corticosteroids, chemotherapy or radiation therapy may be responsible, either singly or in combination (*12,13*).

Corticosteroids are the single most frequent cause of osteonecrosis (*1*). Typically, long-term, high-dose corticosteroid administration is implicated. However, osteonecrosis has been reported in patients receiving short-term corticosteroids for clinical situations including cerebral edema, asthma and septic shock (*14–17,25*). In these cases, the total prednisolone dose ranged from 0.52 gm to 3.4 gm, and was administered during a period of 7 to 32 days (*17*). The interval between corticosteroid administration and onset of symptoms is rarely less than 6 mo and may be more than 3 yr (*1*). Osteonecrosis has also been reported following intra-articular corticosteroid injection (*18*). The pathogenesis of steroid-induced osteonecrosis remains incompletely understood. The most widely accepted mechanism involves steroid-induced changes in fat metabolism and their effects on the precarious subchondral blood supply. Fat embolism and marrow packing with fat, with resultant increase in intraosseous pressure and impeded venous outflow, are two hypotheses related to this concept. Other theories include the role of microfractures and steroid-induced coagulation defects such as sludging and thrombosis (*1,17*).

Chemotherapy alone (systemic and intraarterial) has been implicated as a causative agent in osteonecrosis, but is relatively uncommon (*19–23*). In addition, coadministered corticosteroids and radiation therapy are complicating factors in establishing a causal relationship. Chemotherapy, radiotherapy and corticosteroids may have a synergistic effect in the development of osteonecrosis (*10,13*).

This case report describes the development of multifocal osteonecrosis in a patient receiving chemotherapy and short-term corticosteroids. The relative roles of these risk factors as causative agents are unclear. A synergistic relationship would explain the relatively short time span between corticosteroid administration and onset of symptoms (less than 3 mo). When multiple abnormalities develop on serial bone scanning of the cancer patient receiving chemotherapy with or without corticosteroids, osteonecrosis should be considered in the differential diagnosis, particularly when findings are centered about major joints, are symmetric and are in regions not usually involved in metastatic osseous disease (*24*). Other possibilities include multifocal infection, polysynovitis/arthritis and metastatic disease. MRI is a sensitive and specific modality in the further evaluation of suspected osteonecrosis. Early detection of this condition is necessary in order to prevent irreversible bone and joint destruction.

REFERENCES

1. Mankin HJ. Non-traumatic necrosis of bone (osteonecrosis). *N Engl J Med* 1992;326(22):1473–1479.
2. Pollack MS, et al. Magnetic resonance imaging in the evaluation of suspected osteonecrosis of the knee. *Skeletal Radiol* 1987;16:121–127.
3. Kalunian K, Hahn B, Bassett L. Magnetic resonance imaging (MRI) as a diagnostic tool in ischaemic necrosis of the femoral head in patients receiving glucocorticoids (GC). *Arth Rheum* 1985;28:S36.
4. Totty WG, et al. Magnetic resonance imaging of normal and ischaemic femoral head. *AJR* 1984;143:1273–80.
5. Thickman D, et al. Magnetic Resonance Imaging of avascular necrosis of the femoral head. *Skeletal Radiol* 1986;15:133–40.
6. O'Mara RE. Benign bone disease. In: Gottschalk A, Hoffer PB, Potcher EJ, eds. *Diagnostic nuclear medicine*, 2nd edition. Baltimore: Williams and Wilkins; 1988:1042–1046.
7. Dumont M, Danais S, Taillefer R. "Doughnut" sign in avascular necrosis of the bone. *Clin Nucl Med* 1983;9:44.
8. Gerster JC. Multiple-site avascular necrosis in HIV infected patients. *J Rheumatol* 1991;18:300–302.
9. Enright H, Haake R, Weisdorf D. Avascular necrosis of bone: a common serious complication of allogeneic bone marrow transplantation. *Am J Med* 1990;89:733–738.
10. Mascarin M. Avascular necrosis of bone in children undergoing allogeneic bone marrow transplantation. *Cancer* 1991;68:655–659.
11. Metselaar HJ. Incidence of osteonecrosis after renal transplantation. *Acta Orthop Scand* 1985;56:413–415.
12. Vegna ML. Avascular necrosis of the femoral head in acute leukemia patients treated with combination therapy including steroids. *Eur J Haematol* 1989;42:14–16.
13. Prosnitz LR. Avascular necrosis of bone in Hodgkin's disease patients treated with combined modality therapy. *Cancer* 1981;47:2793–2797.
14. Avital F. Avascular necrosis of bone following short-term dexamethasone therapy for brain edema. A case report. *J Neurosurg* 1984;61:983.
15. Taylor LJ. Multifocal avascular necrosis after short term high-dose steroid therapy: a report of three cases. *J Bone Joint Surg [Br]* 1984;66:431–433.
16. Pfeiffer M, Griss P. Craniocerebral trauma and aseptic osteonecrosis. Steroid-induced sequelae after therapy of brain edema. *Unfallchirurg* 1992; 95(6):284–287.
17. O'Brien TJ, Mack GR. Multifocal osteonecrosis after short-term high-dose corticosteroid therapy. *Clin Ortho Rel Res* 1992;279:176–179.
18. Laroche H, Arlet J, Mazieres B. Osteonecrosis of the femoral and humeral heads after intraarticular corticosteroid injections. *J Rheumatol* 1990;17: 549–551.
19. Pieters R. Osteonecrosis following chemotherapy for leukemia. *Eur J Haem* 1989;43:262–264.
20. Wuisman P. Osteonecrosis of bone associated with intra-arterial therapy using cisplatinum. *Skeletal Radiol* 1991;20:294–298.
21. Harper PG, Trask C, Souhami RL. Avascular necrosis of bone caused by combination chemotherapy without corticosteroids. *Br Med J* 1984;288: 267–268.
22. Obrist R, Hartmann D, Obrecht JP. Osteonecrosis after chemotherapy. *Lancet* 1978;i:1316.
23. Marymont JV, Kaufman EE. Osteonecrosis of bone associated with combination chemotherapy without corticosteroids. *Clin Orthop* 1986;204:150–153.
24. Buskila D. Avascular necrosis of bone mimicking symmetric polyarthritis in a patient with malignant lymphoma treated with high-dose steroids. *Isr J Med Sci* 1992;28:804–805.
25. Healy WL. Osteonecrosis of the knee detected only by magnetic resonance imaging. *Orthopedics* 1991;14(6):703–704.