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Avascular Necrosis of Bone After Adult Acute Lymphocytic Leukemia Treatment With Methotrexate, Vincristine, L-Asparaginase, and Dexamethasone (MOAD)

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Four of 55 (7%) adult acute lymphocytic leukemia patients, age 27–58 years, who were treated with methotrexate, vincristine, L-asparaginase, and dexamethasone (MOAD) developed avascular necrosis (AVN) of one or both femoral heads 16–39 months after beginning treatment. All patients were treated with total joint replacement without compromise of quality of life during more than 3–9 years of follow-up, and they have remained in complete remission for a total of 6.5+ to 10.5+ years. A review of the literature revealed 11 previously reported cases of AVN of bone in patients with acute lymphocytic leukemia, 10 of whom received dexamethasone. The patients in the present report received a total dexamethasone dose equivalent to that of prednisone, 3.4–5.0 g/M². Although AVN of bone has been reported in patients receiving chemotherapy without corticosteroids, corticosteroids appear to be the most common class of agents associated with its development, and dexamethasone treatment may be more likely to result in AVN of bone than other corticosteroids, for unknown reasons.

Key words: adult acute lymphocytic leukemia, avascular necrosis of bone, combination chemotherapy, corticosteroids

INTRODUCTION

Although treatment of adult acute lymphocytic leukemia (ALL) remains difficult, 5-year disease-free survival is currently at about 30% [1]. It is, therefore, important to recognize long-term complications of cure, especially treatable ones, such as avascular necrosis (AVN) of bone.

AVN of bone has been described as a complication of multiple disorders including leukemias, postrenal transplantation, systemic lupus erythematosis, hemoglobinopathy, trauma, psoriasis, hemophilia, and inflammatory bowel disease [2–7]. Since its first description by Ihde and De Vita [8] and subsequently by others [9] as a complication of chemotherapy of lymphoma, AVN of bone has been reported in adolescents with ALL [10–12] but not in older patients. It was thought that adolescent patients were susceptible to the development of bone AVN, secondary to a physiologic increase in steroids or to increased mechanical stress due to greater physical activity [12]. We report here our experience with AVN occurring in 4 of 55 patients treated with methotrexate, vincristine, L-asparaginase, and dexamethasone (MOAD) [1] as initial treatment for adult ALL.

MATERIALS AND METHODS

MOAD is a nonanthracycline-containing regimen that yields state-of-the-art results [1]. The regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) includes five phases: induction, consolidation, cytoreduction, maintenance, and central nervous system prophylaxis with parenteral high-dose methotrexate. Fifty-five patients were treated with MOAD in several institutions [1], and 4 patients developed AVN of bone. Hospital charts were reviewed, and physicians who followed those 4 patients were interviewed. A literature search was per-

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TABLE I. Patient Characteristics

Patient	Age (years)/ sex	AVN site	Diagnosis[a]	Total steroid dose (g/M^2)[b]	Interval from start of Rx to AVN symptoms (months)	CR duration (years)	Posthip surgery follow-up (years)
M.S.	30/M	Hips	T-ALL	5.0	16	10.5+	9.0+
P.P.	58/F	Hip	cALL	4.7	28	9.0+	6.5+
S.W.	38/F	Hips	T-ALL	3.4	39	7.0+	3.0+
J.M.	27/M	Hip	T-ALL	3.8	14	6.5+	4.0+

[a]T-ALL, T-cell acute lymphocytic leukemia; cALL, common acute lymphocytic leukemia; ALL-NOS, acute lymphocytic leukemia, not otherwise specified.
[b]As equivalent dose of prednisone.

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RESULTS

Characteristics of the patients who developed AVN of bone are summarized in Table I.

Case 1

M.S. is a 30-year-old male, diagnosed with T-cell ALL by peripheral blood and bone marrow phenotyping in May 1984 when he had a palpable spleen and an enlarged axillary lymph node. His white blood cell count was 50,000/mm^3 with 96% immature lymphocytes, hematocrit 21%, and platelet count 35,000/mm^3. The patient was treated with MOAD [1] and achieved complete remission after two cycles of induction treatment. In November 1984 he had an isolated central nervous system relapse which was treated with intrathecal methotrexate. As of January, 1996 his leukemia has remained in complete remission.

In September 1985 the patient complained of increasingly severe right hip pain. An X-ray of the hips suggested early osteonecrosis, and a bone scan showed increased uptake in both hips. He had bilateral total hip replacements in November 1985, and pathologic examination of the femoral head revealed AVN. The patient became fully functional within a month of his surgery and has worked daily at his regular employment for more than 9 years since, during which time he has remained free of leukemia, and asymptomatic with respect to his hips.

Case 2

P.P., a 58-year-old woman, presented in July 1986 with fever, oral thrush, and lymphadenopathy. Laboratory data included a white blood cell count of 2,300/mm^3, with 71% lymphocytes and 1% blasts, a platelet count of 62,000/mm^3, and a right lower-lobe infiltrate on chest X-ray. A bone marrow examination was morphologically and immunophenotypically diagnostic of common ALL. She was treated with MOAD and, in addition, received intrathecal methotrexate for meningeal leukemia diagnosed by lumbar puncture, and achieved complete remission after three cycles of treatment.

In late 1987 the patient developed bilateral knee pain which gradually progressed to the point that she required assistance with ambulation. She subsequently underwent bilateral knee joint replacement for degenerative joint disease. In November 1988 she developed left hip pain, and X-rays of the hips revealed a crescent rim of sclerosis with a central lucency in the left femoral head suggesting AVN. A bone scan showed increased uptake in the left hip only. In March 1989 the patient had a left total hip replacement for pathologically documented AVN of the femoral head. She has continued in complete remission for more than 9 years, and is fully functional, active, and asymptomatic more than 6.5 years after hip surgery.

Case 3

S.W., a 38-year-old woman, presented in July 1988 with multiple ecchymoses and abdominal pain. Laboratory studies revealed a white blood cell count of 159,000/mm^3 immature lymphocytes, platelet count 40,000/mm^3, hemoglobin 5.5 g/dl, and a bone-marrow aspirate diagnostic of T-cell ALL. The patient was started on MOAD and was in complete remission after three cycles of induction treatment.

In October 1991 she developed progressive right hip pain and required crutches by early 1992. In July 1992 bone scans of both hips were positive, and sclerotic densities were noted on X-ray and on magnetic resonance imaging. She had a right total hip replacement in October 1992, and the same procedure on the left hip 6 months later. Pathologic findings at both operations were diagnostic of AVN of the femoral heads. She has continued in complete remission for more than 7 years, and is fully functional and asymptomatic 3 years after hip surgery.

Case 4

J.M., a 27-year-old male, presented in December 1989 with a palpable spleen and a mediastinal mass on chest X-ray. Laboratory examination disclosed a white blood cell count of 70,000/mm^3 with 50% lymphoblasts, and normal hemoglobin and platelet counts. A bone-marrow

aspirate was diagnostic of T-cell ALL. The patient was started on MOAD, and was in remission after two cycles of induction treatment.

In January 1991 the patient complained of pain in the right hip, and an X-ray showed destruction of the femoral head. A total hip replacement was performed in November 1991, and AVN of the femoral head was confirmed by pathologic examination. The patient has remained free of leukemia for more than 6.5 years, is fully functional, and has worked regularly more than 4 years postsurgery.

DISCUSSION

Bone pain occurs in as many as 50% of patients with acute leukemia, especially those with ALL [11]. The differential diagnosis includes bone involvement by leukemia, especially in childhood ALL [13], but bone infiltration by leukemia is also well-documented in chronic myelocytic [2] and hairy-cell [3] leukemia. Bone-marrow necrosis is associated with a poor prognosis in acute leukemia, and is an uncommon cause of bone pain in leukemia patients [14]. Joint pain occurs much more commonly than other bone pain in patients with leukemia and may be due to hyperuricemia [15], leukemic joint infiltration [15], and, rarely, AVN. On occasion, metabolic bone disease in ALL is painful [16].

AVN of bone may be a complication of chemotherapy either with or without steroids [8–12,17–19]. The most commonly involved site is a weight-bearing joint such as the hip [20,21]. The incidence of AVN of bone may be as high as 10% at 10 years in those treated with steroid-containing regimens [21,22]. AVN of bone in cancer patients was first reported in those with malignant lymphoma treated with MOPP [8,9], and later in adolescents with ALL treated with steroid-containing regimens [10–12] (Table II). The relationship between AVN of bone and steroid total dose cannot be determined, since reported dosages range from 2–11 g [10], which are significantly lower than doses used in organ transplantation [20]. The interval from initiating steroids to onset of symptoms is reported to range from 6–78 months [8–12,22].

Other agents possibly responsible for AVN in patients treated with nonsteroid-containing regimens are bleomycin and vinblastine in testicular embryonal carcinoma [17], doxorubicin, methotrexate, and 5-fluorouracil in breast cancer [18], cyclophosphamide in lymphoma [8], and methotrexate in ALL [19]. Although the reported methotrexate-treated ALL children were also treated with prednisone, the episodes of AVN were clearly related to maintenance methotrexate treatment, as the bony disorders responded to methotrexate withdrawal [19]. However, methotrexate administration may be more likely to result in bone fracture or impaired fracture healing than AVN [23]. In our patients the most likely cause of AVN was steroids because of the lack of symptomatic improvement after methotrexate withdrawal.

The pathogenesis of AVN of bone is unclear. Spencer et al. [24] observed that the initial lesion is a reduction of the total number of osteocytes, which may result from the direct cytotoxic effect of drugs or from interference with intraosseous microcirculation, followed by medullary necrosis, separation of necrotic focus, and, eventually, collapse of the femoral head. Wang et al. [25] reported that hypertrophic marrow fat cells or fat emboli caused a rise in intraosseous pressure and resultant AVN in a cortisone-treated rabbit model. Others suggest that occlusion of the epiphyseal vessels by hemarthrosis in patients with hemophilia [6], impairment of bone circulation in hemoglobinemia and hyperlipidemia [4], peripheral neuropathy in diabetes [26] and vinca alkaloid treatment [27], renal allograft dysfunction or rejection [28,29], and cyclosporine administration [30] may play a role in the etiology of AVN of bone. All may have common final pathways, and are not mutually exclusive [31].

Radioisotope bone scans and magnetic resonance imaging studies may be positive months before symptoms of AVN [32,33]. Radiographic stages were first proposed by Ficat [34], but more recently others have employed systems utilizing magnetic resonance imaging techniques [35,36]. In those patients at high risk for AVN but with negative magnetic resonance imaging studies, Koo et al. [37] have used angiography, intraosseous pressure, and core biopsy to diagnose subclinical AVN.

Although no consensus has been reached concerning the relative merits of early and late treatment [33], some advocate early intervention. Ficat [34] reported that clinical results of core decompression are better in earlier stages of AVN. Stulberg et al. [38] randomized 55 AVN hips to core decompression or conservative treatment. They reported longer median survival of the femoral head and lower arthroplasty rates in the core decompression group, compared with those treated conservatively. Others recommend only conservative treatment initially, such as relief of weight-bearing where appropriate, physiotherapy, and analgesics [39].

The patients reported here and in Tables I and II demonstrate that bone AVN is an uncommon yet debilitating complication of therapy for ALL in children and adults. The remarkable results achieved with early total joint replacement in our patients suggest that such early intervention is highly appropriate. Since half of the patients in Tables I and II are T-ALL compared with a 24% and 13% incidence of T-ALL in adult and childhood ALL, respectively [40], the question arises as to whether bone AVN is more frequent in T-ALL compared with other phenotypes. Future studies should address this question.

TABLE II. Previously-Reported ALL Patients With AVN

Reference (no. of patients)	Age (years)/sex	AVN site	Diagnosis[a]	Total steroid dose (g/M^2)[b]	Interval from diagnosis to AVN symptoms (months)	CR duration (years)
10 (1)	18/F	Hip	cALL	7.6 g, total dose	22	2+
11 (5)	15–25/M	Hips, 2 Knees, 4 Ankles, 2	cALL-2 B-ALL-1 T-ALL-2	5.1–8.3	7–18	2+–8+
12 (5)	10–17/M, 2; F, 3	Hips, 11 Elbows, 3 Ankles, 2	ALL-NOS	5.3–8.4	8–18	"1-year relapse"

[a]T-ALL, T-cell acute lymphocytic leukemia; cALL, common acute lymphocytic leukemia; ALL-NOS, acute lymphocytic leukemia, not otherwise specified.
[b]As equivalent dose of prednisone.

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