Avascular Necrosis of the Femoral Head in Children With Acute Lymphoblastic Leukemia: A 4- to 9-year Follow-up Study

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abstract

Avascular necrosis of the femoral head is usually seen in children aged 1.5 to 10 years, reaching a peak incidence between the ages of 4 and 9. Avascular necrosis of the femoral head is a known complication of corticosteroid therapy in acute lymphoblastic leukemia. There are few reports in the literature regarding the natural history of this condition, and there is no consensus on its management. This study examined the natural history of avascular necrosis of the femoral head in children with leukemia.

From 1993 to 2006, a total of 865 children with acute lymphoblastic leukemia were admitted to the hematology-oncology ward of a children's hospital. The diagnosis of acute lymphoblastic leukemia was established by bone marrow aspiration. Based on clinical and radiographic findings, avascular necrosis of the femoral head was found in 7 patients; these patients underwent follow-up for 4 to 9 years. Avascular necrosis of the femoral head was clinically symptomatic in all of the children, and they had advanced radiographic collapse of the femoral head. However, the head of the femur was not at risk in any patient based on clinical and radiographic findings. Patients received supportive treatment such as abduction brace and physiotherapy. After 4 to 9 years of follow-up, clinical and radiographic results were satisfactory. Provided that the head of the femur is not at risk, avascular necrosis of the femoral head in children with acute lymphoblastic leukemia may be successfully managed with nonoperative care.
Avascular necrosis of the femoral head is usually seen in children aged 1.5 to 10 years, reaching a peak incidence between the ages of 4 and 9. This condition can be either idiopathic or secondary to several known causative factors, namely, trauma, blood disorders, hip infections during infancy, and iatrogenic etiologies.\(^1\)

Bone necrosis in avascular necrosis of the femoral head is confined to the femoral head and is produced by direct cellular toxicity or vascular compromise. Chemotherapy and systemic steroid use can cause avascular necrosis of the femoral head by direct cellular toxicity.\(^2\)

Patients with avascular necrosis of the femoral head are initially asymptomatic, but gradually, they experience pain associated with activity in the hip joint. Limping and restricted hip motions are noted with disease progression. Without any therapeutic intervention, avascular necrosis of the femoral head can run its course toward progressive deterioration. However, depending on the stage of the disease, different treatment strategies can be applied to reduce the symptoms and improve the functional capacity of patients.\(^1,2\)

One of the precipitating conditions leading to avascular necrosis of the femoral head in children is acute lymphoblastic leukemia.\(^1,4\) The high frequency of avascular necrosis in children with leukemia is attributed to the intensive steroid therapy regimens.\(^5\) Acute lymphoblastic leukemia is the most common malignancy during childhood, with a peak incidence between the ages of 3 and 5. Avascular necrosis of the femoral head can affect 0.5% to 1% of patients with acute lymphoblastic leukemia.\(^5\)

There are few reports in the literature regarding the natural history of avascular necrosis of the femoral head, and there is no consensus on its management. This prospective study examined the clinical course of avascular necrosis of the femoral head and its outcome in children with acute lymphoblastic leukemia.

**Materials and Methods**

From 1993 to 2006, a total of 865 children with the diagnosis of acute lymphoblastic leukemia were admitted to the hematology-oncology ward of a children’s hospital. The diagnosis of acute lymphoblastic leukemia was established by bone marrow aspiration. Patients were divided into standard-risk and high-risk groups based on uniform criteria, especially age and white blood cell count.\(^6\)

The treatment protocol consisted of induction for 4 weeks with vincristine, prednisone (2 mg/kg/day), L-asparaginase, and doxorubicin. The prednisone was tapered and discontinued, followed by 7 to 10 days of consolidation with L-asparaginase, cytarabine, and VP-16. Central nervous system prophylaxis included intrathecal injections of methotrexate, hydrocortisone, and cytarabine with intravenous infusion of high-dose methotrexate for standard-risk patients and cranial radiotherapy for high-risk patients.

Maintenance consisted of daily oral 6-mercaptopurine and weekly oral methotrexate, weekly L-asparaginase for 16 weeks, vincristine, and prednisone (2 mg/kg/day) every 3 weeks for standard-risk patients, and vincristine, prednisone, and cyclophosphamide every 4 weeks for high-risk patients. This stage of maintenance was followed by 4 weeks of induction with vincristine, daunomycin, and dexamethasone (0.1 mg/kg/dose every 6 hours). Dexamethasone then was tapered and withdrawn. Maintenance therapy was continued for up to 2 years as follows: intravenous vincristine and oral prednisone (2 mg/kg/day for 5 days, with a maximum dose of 60 mg/day) every 3 weeks for the standard-risk group; high-risk patients received one dose of cyclophosphamide along with vincristine and prednisone every 4 weeks. After 2 years of intravenous treatment, maintenance therapy was replaced with an oral regimen of weekly methotrexate and daily 6-mercaptopurine for 1 year. Overall, the total duration of maintenance was 3 years.

Based on clinical and radiographic findings, avascular necrosis of the femoral head was found in 7 patients. The date of the earliest reported radiograph was regarded as the date of diagnosis of avascular necrosis of the femoral head (Figure 1). Each patient’s gender and age at the time of diagnosis of acute lymphoblastic leukemia and avascular necrosis of the femoral head were noted. Limping, amount of reduction in hip motions, and the radiographic stage (using the University of Pennsylvania classification)\(^7\) of avascular necrosis of the femoral head in anteroposterior (AP) and frog-leg pelvic views were recorded. Radiographs were reviewed by an orthopedic surgeon and a radiologist, who were in agreement on the diagnosis and staging of avascular necrosis of the femoral head. Patients’ clinical progress was monitored by physical and radiographic examination every 3 months until the resolution of clinical and radiographic signs and symptoms.

At the end of follow-up in 2003, clinical and radiographic data of patients were reassessed (Figures 2, 3). Radiographic grade of remodeling of the femoral head was evaluated according to the classification of Stulberg et al.\(^8\) Two patients died in 2002 from relapse of acute lymphoblastic leukemia, but their data had been recorded before death. Findings at the last follow-up examination were compared to those at the time of diagnosis of avascular necrosis of the femoral head.
RESULTS

Mean age for the 7 patients (4 boys and 3 girls) with avascular necrosis of the femoral head was 10.2 years (range, 5-13 years) at the time of diagnosis of acute lymphoblastic leukemia. The median interval from the diagnosis of acute lymphoblastic leukemia to the diagnosis of avascular necrosis of the femoral head was 20 months (range, 10-91 months). Avascular necrosis of the femoral head occurred during the relapse phase in 2 patients. Patient characteristics are summarized in the Table.

After completion of chemotherapy, all patients entered the remission phase. Four patients later had recurrence of acute lymphoblastic leukemia; during treatment of the recurrence, 1 patient died at age 16. Another patient died from *Pneumocystis carinii* pneumonitis infection. All of the patients experienced hip pain or limping, and they had limitation of hip motion and radiographic findings of avascular necrosis at the time of diagnosis of avascular necrosis of the femoral head. During the course of avascular necrosis of the femoral head, radiographic assessment of the femoral head, both on AP and frog-leg views, showed avascular necrosis stage III in 1 patient and avascular necrosis stage IV in the remaining 6 patients. All 7 patients were treated nonoperatively with conservative methods (eg, walking correctly, no jumping, using Scottish Rite abduction brace).

Average follow-up was 81.8 months (range, 48-115 months). Patients were checked for the possible development of osteoporosis during follow-up, and they received supportive treatments, such as abduction brace, physiotherapy, and calcium or vitamin D supplements, as needed. At their last examination, 2 patients were limping and 1 patient had limited rotational hip motion. However, symptoms improved in all of the patients, and significant remodeling of the femoral head was evident radiographically. Three patients had grade I and 4 patients had grade II remodeling according to Stulberg’s classification. Remodeling was more complete in boys compared to girls (Table).

DISCUSSION

Little is known about the pathogenesis of acute lymphoblastic leukemia, although both inheritance and specific environmental exposures are believed to play a role in this process. More children in developing countries such as Iran live near high-voltage lines, and they experience relatively more harmful effects from the magnetic fields compared to children in developed countries, which results in a higher prevalence of young patients with acute lymphoblastic leukemia in developing countries.9

Avascular necrosis is a potentially disabling complication of chemotherapy including high doses of steroids that is seen in patients with leukemia and lymphoma. Other factors, such as immobilization or

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Risk Group</th>
<th>AVNFH Stage</th>
<th>Symptoms</th>
<th>Side of Hip Involvement</th>
<th>Duration of Symptom Improvement</th>
<th>Grade of Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/10</td>
<td>High</td>
<td>IV</td>
<td>Limp</td>
<td>Bilateral</td>
<td>7 months later</td>
<td>II</td>
</tr>
<tr>
<td>2/M/13</td>
<td>High</td>
<td>IV</td>
<td>Limp, hip and wrist pain</td>
<td>Left</td>
<td>6 months later</td>
<td>I</td>
</tr>
<tr>
<td>3/F/5</td>
<td>Standard</td>
<td>IV</td>
<td>Hip and ankle pain</td>
<td>Bilateral</td>
<td>6 months later</td>
<td>II</td>
</tr>
<tr>
<td>4/M/12</td>
<td>High</td>
<td>III</td>
<td>Limp</td>
<td>Bilateral</td>
<td>6 months later</td>
<td>I</td>
</tr>
<tr>
<td>5/M/9</td>
<td>Standard</td>
<td>IV</td>
<td>Limp, knee pain</td>
<td>Bilateral</td>
<td>22 months later</td>
<td>II</td>
</tr>
<tr>
<td>6/M/12</td>
<td>High</td>
<td>IV</td>
<td>Limp, ankle pain</td>
<td>Left</td>
<td>5 months later</td>
<td>I</td>
</tr>
<tr>
<td>7/F/11</td>
<td>High</td>
<td>IV</td>
<td>Limp</td>
<td>Left</td>
<td>Surgery recommended</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AVNFH, avascular necrosis of femoral head.
malignancy itself, may contribute to the development of avascular necrosis. Steroids are the second most common cause of avascular necrosis after trauma. The mechanism of action associated with corticosteroids and development of avascular necrosis is unclear, but several effects such as increased osteoblast and osteoclast apoptosis and increased coagulation protein concentrations have been postulated.

As more children with acute lymphoblastic leukemia survive into adulthood, orthopedists are increasingly called on to manage avascular necrosis affecting multiple joints. Avascular necrosis of bone is usually multifocal, and weight-bearing joints are predominantly affected. In practice, however, the femoral head is the most symptomatic site that often requires surgical intervention.

Avascular necrosis can be managed by surgical or pharmacologic treatment options. Goals of avascular necrosis management are typically palliative, as there is currently no proven treatment available to stop progression of the disease. Avascular necrosis of the femoral head can deteriorate the quality of life in patients with acute lymphoblastic leukemia, which has become an almost curable hematologic condition. Traditionally, treatment of avascular necrosis of the femoral head includes some type of surgery, but undertaking an operative procedure in high-risk patients is not without hazards.

Our study supports reports of previous authors that steroid-induced avascular necrosis of the femoral head may be successfully managed without any intervention as long as femoral head is not at risk.

A few authors have reported that avascular necrosis of the femoral head may run a mild course in patients with acute lymphoblastic leukemia depending on the site and size of the lesion. Lafforgue confirmed corticosteroid therapy as one of the major causes of avascular necrosis of the femoral head in patients with acute lymphoblastic leukemia. He suggested nonoperative treatment only for patients in whom the lesion was limited to the nonweight-bearing region of the femoral head and in whom the acetabulum was intact. In such patients, avascular necrosis of the femoral head improved only if the precipitating factor, such corticosteroid therapy or acute lymphoblastic leukemia itself, was eliminated.

Steinberg et al showed that when the necrotic area was small, and particularly when it was located in the nonweight-bearing area of the femoral head and the patient was clinically asymptomatic, avascular necrosis of the femoral head can have a good course. However, the majority of clinically symptomatic patients in their study had progressive collapse of the femoral head with no operative intervention. For such patients, symptomatic therapy, such as the use of a cane or brace, was not effective.

In another study, Ojala et al reported that 9 patients with acute lymphoblastic leukemia showed spontaneous regression and even complete healing of osteonecrotic lesions. None of their patients required interventional treatments based on magnetic resonance imaging (MRI).

In contrast, there are reports that avascular necrosis of the femoral head is persistently progressive regardless of the size and site of the lesion. Beguin et al reported 3 cases of avascular necrosis of the femoral head among 266 children undergoing chemotherapy for acute lymphoblastic leukemia. Despite early diagnosis and immediate management of avascular necrosis of the femoral head, osteonecrosis was progressive in all of the patients, causing limb shortening and limited motion in the affected hip.

In their study of avascular necrosis of the femoral head caused by chemotherapy in 85 children with acute lymphoblastic leukemia, Vaidya et al diagnosed 5 cases of avascular necrosis of the femoral head. In all 5 patients, the course of the disease was progressive, and 3 patients needed operative intervention.

Solarino et al reported a 14-year-old girl who developed multifocal osteonecrosis after treatment with chemotherapy and corticosteroids for acute lymphoblastic leukemia. Six months after beginning treatment, the patient was diagnosed with avascular necrosis of the left knee, and both hips and shoulders. The patient underwent bilateral total hip arthroplasty, which was still functioning well at the last follow-up visit at 5.3 years.

There are few reports concerning children with steroid-related bone avascular necrosis with spontaneous resolution. In addition, there are few studies in the orthopedic literature regarding the course of avascular necrosis of the femoral head in patients with leukemia.

In our study, although all of the patients had advanced stages of femoral head collapse, they had a benign course to become almost asymptomatic and developed nearly complete head regeneration. Based on clinical and radiographic findings, the femoral head was not at risk in any of our patients when the diagnosis of avascular necrosis of the femoral head was established. On the other hand, the oncologists believed it was not safe to taper the steroid dose in any of the patients at the time of diagnosis of avascular necrosis of the femoral head. Therefore, patients received only nonoperative care consisting of temporary abduction brace, physical therapy, and anti-inflammatory drugs.

One of the limitations of this study is the small number of patients. We therefore could not draw any statistical significance from our findings regarding the effect of gender or age on the development of avascular necrosis. Moreover, we acknowledge that some cases of avascular necrosis might have been underdiagnosed given that radiographs or MRI were not routinely obtained for asymptomatic patients at our institution. The study patients were primarily from a low socioeconomic status being treated in a university hospital. Having received no funds for the study,
we did not impose the costs of MRI on the families of these patients.

Overall, physicians need to have a higher index of suspicion for this complication in patients with acute lymphoblastic leukemia so that diagnostic and therapeutic procedures are initiated at a proper time. Future studies with larger number of patients are needed.

REFERENCES