Avascular Necrosis of Bone in Children With Leukemia

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Abstract

Avascular necrosis of the bone (AVNB) is an uncommon serious complication of acute leukemia. Between the years 1997-2007, seven children with acute leukemia of different risk groups presented with symptoms, signs and investigational evidence of avascular necrosis of bone. They were all diagnosed during their maintenance chemotherapy except one patient who had AVNB post-transplant following hematological relapse. Six patients had avascular necrosis of the hip (AVNH), and one patient had avascular necrosis of the foot. Other complications for steroids, such as hyperglycemia were observed in some of the patients. The steroids were omitted in almost all patients immediately. Two patients had surgical intervention and the rest received conservative management. Two patients recovered fully and the rest are still under follow-up at orthopedic clinic pending further management.

Key words

Avascular necrosis of the bone, avascular necrosis of the hip, leukemia, BMT, steroid therapy

Introduction

Avascular necrosis is a serious complication of many chronic and other medical diseases. It is however uncommon in acute leukemia in children. It usually affects the femoral hip but it has been reported in other joints. Avascular necrosis is multi-factorial: It can happen due to the disease process per se or could be a result of a corticosteroid therapy. In this report, we describe the occurrence of avascular necrosis in seven children with acute leukemia, who developed the disease during their maintenance chemotherapy treatment.

Cases Reports

NBK Hematology unit at Al-Sabah hospital is the only medical center in Kuwait that manages pediatric leukemias, receiving on average 36 new cases per year. The yearly incidence of Leukemia in Kuwait is 5 new cases per 100,000 of children below the age of 14 yrs. Seven children known to have acute leukemias, and on maintenance chemotherapy, presented to NBK pediatric hematology unit at Al-Sabah Hospital, between the years 1997-2007, with symptoms and signs suggestive of avascular necrosis of bone (AVNB). They were three girls and four boys, the eldest aged 13.5 years old and the youngest aged 3.5 years, with average age of 10.2 years (Table 1). Patients 1, 4, and 7 received standard risk protocols, while patients 2, 3, and 5 received high risk protocols. Dexamethasone is the steroid of choice used in the chemotherapy protocols. The dose given varied during the intensive chemotherapy treatment. In general the highest and prolonged doses of dexamethasone given during the intensive ALL chemotherapy protocol were 6mg/m²/day for four weeks during induction, and 10mg/m²/day for two weeks during each of the two delayed intensification courses, otherwise short courses of dexamethasone were given repeatedly during the entire chemotherapy treatment. Only one patient (patient 6) had an aggressive course of his AML disease as he had hematological relapse while on maintenance chemotherapy. He required bone marrow transplant (BMT), and therefore received further doses of steroids. He developed AVNB during the first post BMT year, and just before tapering the steroid therapy. All patients presented with few days history of limping and pain. X-rays were done to the affected sites and were reviewed by radiologists, and later had more specific radio-imaging. All patients were followed up at our out patient clinic and had clinical examinations...
as well as lab investigations taken regularly.

Results

Almost all patients had avascular necrosis of the femoral head (AVNH), two patients (patient 5 and 6) developed the disease bilaterally, and only one child had avascular necrosis (AVNB) involving the foot. There were other complications observed in patients throughout the course of leukemia treatment, which were related to steroid therapy, such as obesity, and hyperglycemia. Obesity was observed in four patients, and two patients had steroid induced hyperglycemia (Table 1). Patient 2 is diabetic undergoing insulin replacement therapy under the care of an adult diabetologist. Patient 7 had recurrent foot ulcers all through his maintenance chemotherapy course.

The diagnosis was confirmed in each patient with MRI study, except for one patient where bone scan was used instead. All patients were referred to orthopedic specialists: five patients were treated conservatively, while two patients underwent surgery (Table 1). The steroid therapy courses were immediately either omitted or slowly tapered and stopped from the rest of the chemotherapy protocol for most of the patients. Patient 7 has just completed his chemotherapy according to his protocol, when he was diagnosed with AVNB.

All patients are now in remission and have successfully completed their chemotherapy according to their protocol. Two boys (patient 1 and 2) have a remarkable full improvement from AVNB: patient 1 received conservative treatment, and patient 2 underwent a surgery for avascular necrosis of hip. The rest of the patients had partial improvement of avascular necrosis of bone, and most are still limping. The decisions to go for hip replacements were postponed until adulthood (Table 1).

Discussion

There are multiple causative factors for necrosis of bone. Studies performed in patients, related avascular necrosis of the hip (AVNH) to intensive corticosteroid therapy, however have shown that AVNH can occur for a variety of reasons that could be local or systemic(4). Acute leukemia can be a causative factor even before the start of chemotherapy(5). Other factors for the development of AVNB should be considered such as prolonged bed rest, avoidance of sun exposure due to multiple hospital admission, obesity and poor diet as well as loss of appetite. Furthermore, most patients have a restrictive diet to avoid infections. These patients received massive chemotherapy medications. The total effect of these medications on the pathway of vitamin D and calcium metabolism

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age in Years</th>
<th>Diagnosis</th>
<th>Other complications during chemotherapy treatment</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1</td>
<td>Male</td>
<td>6.5</td>
<td>Acute Lymphocytic Leukemia, PreB-ALL</td>
<td>Two admission for febrile neutropenia</td>
<td>Surgery; core decompression of the left femoral head</td>
</tr>
<tr>
<td>Pt2</td>
<td>Male</td>
<td>12.3</td>
<td>Acute Lymphocytic Leukemia, PreB-ALL</td>
<td>Steroid induced hyperglycaemia</td>
<td>Conservative</td>
</tr>
<tr>
<td>Pt3</td>
<td>Female</td>
<td>13.5</td>
<td>Acute Lymphocytic Leukemia, PreB-ALL</td>
<td>Steroid induced hyperglycaemia Psychosis</td>
<td>Conservative</td>
</tr>
<tr>
<td>Pt4</td>
<td>Female</td>
<td>10.5</td>
<td>Acute Lymphocytic Leukemia, L1-ALL</td>
<td>No records</td>
<td>Left valgus extension femoral osteotomy</td>
</tr>
<tr>
<td>Pt5</td>
<td>Female</td>
<td>13.3</td>
<td>Acute Lymphocytic Leukemia, L2- ALL, Biphenotype</td>
<td>Acute renal failure during induction</td>
<td>Conservative</td>
</tr>
<tr>
<td>Pt6</td>
<td>Male</td>
<td>12.0</td>
<td>Acute Myeloid Leukemia M1/relapse/BMT</td>
<td>CGVHD</td>
<td>Conservative</td>
</tr>
<tr>
<td>Pt7</td>
<td>Male</td>
<td>3.5</td>
<td>Acute Lymphocytic Leukemia, PreB-ALL</td>
<td>Recurrent foot ulcer</td>
<td>Conservative</td>
</tr>
</tbody>
</table>

Average age=10.2yrs

Table 1: Patients vital data
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is still unknown. This is true for patients who received intensive prolonged chemotherapy courses containing high and repeated doses of steroids. One of our patients received prolonged chemotherapy course, then after his first hematological relapse underwent bone marrow transplant, and was followed by further doses of steroid. This patient developed AVNH bilaterally during his first BMT year(6).

In our practice, it has been observed that all patients suffered from other complications of steroid therapy such as obesity and hyperglycemia, and even psychosis. The presentation of AVNB was late in the course of the disease and treatment. This may suggest the possibility that the disease was subtle for some time, or perhaps the symptoms of AVNB have been overlooked.

Patient 7 developed recurrent foot ulcer with skin culture positive for bacterial infection, which was difficult to manage medically. This emphasizes the role of infection as a possible causative factor. Unfortunately we could not find evidence in the literature relating skin infection to necrosis of the bone.

Enhanced magnetic resonance (MRI) imaging is the most sensitive tool for early diagnosis of AVNB(8-9). All patients were diagnosed with MRI, with the exception of one patient who was diagnosed by a bone scan as she was initially was suspected to have osteoarthritis(7). Unfortunately we do not have full details of the extent of the femoral head necrosis in each patient. This could have added more insight to the association between the steroid doses, the aggressiveness of leukemia versus the severity of the avascular necrosis of the bone (AVNB). In this study we proposed considering MRI studies for all patients with risk factors such as prolonged chemotherapy course with high dose steroid and obesity, in an attempt to diagnose subtle AVNB.

The surgical alternatives may include core compression, osteotomy, non-vascularized and vascularized bone grafting, which might be enhanced with the use of growth and differentiation factors(10). The goal in the treatment of osteonecrosis of the femoral head is to preserve, not to replace the femoral head(11). Our patients were followed by orthopedic specialist in and out the state of Kuwait. Two of our patients had surgical intervention: one patient had osteotomy and the other had core decompression.

Prophylaxis with bisphosphonate may be worthwhile in certain patients for the early management of pain due to AVNH; however surgical intervention is warranted in the treatment of osteonecrosis eventually(8). Most of our patients recovered with supportive treatment, which included analgesia and avoidance of weight bearing. Awareness of this complication is important in order to have an early diagnosis so as to limit disability(12).

**Conclusion**

Although the occurrence of avascular necrosis of the bone (AVNB) is mostly related to higher doses of corticosteroids during intensive chemotherapy courses in children with leukemia, other causes should not be overlooked such as diet, activity and infection. We should have a higher level of suspicion in patients with risk factors such as patients receiving high steroid doses or obese children, and MRI should be considered for such cases. In addition we should consider a bone lesion (AVNB) in any patients with recurrent localized skin infection.
References


