High-dose steroid-related osteonecrosis in a four-year-old child with acute lymphoblastic leukemia

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ABSTRACT

Osteonecrosis is an uncommon complication of acute lymphoblastic leukemia. One of the risk factor is high-dose corticosteroid therapy. The highest incidence of osteonecrosis is observed in children 9 to 18 years old at diagnosis and it is a rare condition below 5 years of age. We describe a 4 year-old child with acute lymphoblastic leukemia and complaints of progressive bone pain and walking difficulty who developed osteonecrosis and bone fracture after two remission induction chemotherapy.

Key Words: Osteonecrosis, Corticosteroid, Acute lymphoblastic leukemia, Treatment.

ÖZET

Akut lenfoblastik lösemili dört yaşında bir çocukta yüksek doz steroide bağlı osteonekroz

Osteonekroz akut lenfoblastik löseminin nadir bir komplikasyonudur ve yüksek doz steroid tedavisinin risk faktörlerinden biridir. En yüksek osteonekroz insidansı tanı anında 9-18 yaşları arasında olan çocuklarda görülmektedir ve beş yaş altında nadirdir. Biz akut lenfoblastik lösemi nedeniyle iki kez remisyon indüksiyon kemoterapisi aldıktan sonra kemik ağrısı ve yürümede güçlük yakınması başlayan ve diz ekleminde osteonekroz ve fraktür gelişen dört yaşında bir olgu sunduk.

Anahtar Kelimeler: Osteonekrozis, Kortikosteroid, Akut lenfoblastik lösemi, Tedavi.

INTRODUCTION

Osteonecrosis is a potentially disabling complication of cancer treatment[1]. Osteonecrosis may be asymptomatic but may also cause severe pain, joint swelling, limited range of motion, and ultimately joint damage and articular collapse. Osteonecrosis is usually multifocal and weight-bearing joints are predominantly affected[2]. Although its etiopathogenesis is not fully established, steroids are considered one of the main causative factors[3]. Steroids are also an essential component of chemotherapy in acute lymphoblastic leukemia (ALL). The incidence of symptomatic osteonecrosis in children with ALL was reported as 1.1-9.3% in large series[4-6]. The highest incidence of osteonecrosis is observed in children 9 to 18 years old at diagnosis; it is a very rare condition below five years of age.

We describe a four-year-old child with ALL and osteonecrosis of both femoral and tibial epiphyses, and femoral condyle fracture, which developed after two remission induction chemotherapies.

CASE REPORT

A (four-year-old) boy was referred to our hospital for evaluation of anemia and leukocytosis. The child was healthy until three months before admission, when he started complaining of arthralgia. Pallor was the only abnormality on physical examination. Laboratory findings revealed hemoglobin 4.9 g/dL, white blood cell count 138,000/mm^3, and platelet count 157 x 10^9/L. Bone marrow aspiration showed 95% blast cells that were characteristic of ALL, with L1 type morphology. Periodic acid-Schiff stain was positive and peroxidase was negative on bone marrow aspiration smear. We found CD10 and CD19 values to be positive, whereas CD5, CD7, CD20 values were negative on flow cytometry. We were not able to examine chromosomal analysis because of technical insufficiency. All the biochemical test results were within normal range, except for elevated serum lactate dehydrogenase (1571 U/mL).

With all these data, morphologically L1 and immunologically preB type ALL was diagnosed. The patient was treated with the previously described modified St. Jude Total Therapy Studies XIII with minor modification including high-dose methylprednisolone (HDMP)[7]. HDMP was administered during remission induction treatment (20 mg/kg/day in the first week, 10 mg/kg/day in the second week and 2 mg/kg/day in the last two weeks). A total of 4760 mg/m^2 prednisolone was given within 28 days. Remission induction treatment could only be completed within 40 days due to neutropenic sepsis attack. The patient was readmitted for the consolidation treatment 45 days after remission induction therapy, which was 30 days later than originally planned. Bone marrow aspiration showed 30% lymphoblasts. Due to the patient's noncompliance with the treatment regimen, repeated remission induction treatment including HDMP was attempted and remission was successfully achieved. According to the chemotherapy protocol, 4760 mg/m^2 prednisolone was given again within 30 days.

At the end of the second remission induction treatment, bone pain and walking difficulty started. T1 and T2 weighted magnetic resonance images (MRI) showed hypointense foci of osteonecrosis associated with larger areas of reactive marrow edema of the medial and lateral femoral condyle and tibial plateaus. A fracture of the distal femoral condyle was also detected on MRI (Figure 1 A,B). Orthopedic surgical intervention for femoral condyle fracture could not be performed because of the patient's poor general condition. The patient died due to neutropenic sepsis which occurred one month after the second induction treatment.

DISCUSSION

Recent advances in intensive multiagent chemotherapy along with adequate supportive care have produced remarkable improvements in long-term survival of children affected by ALL. As cure rates have improved, research has focused on the recognition and

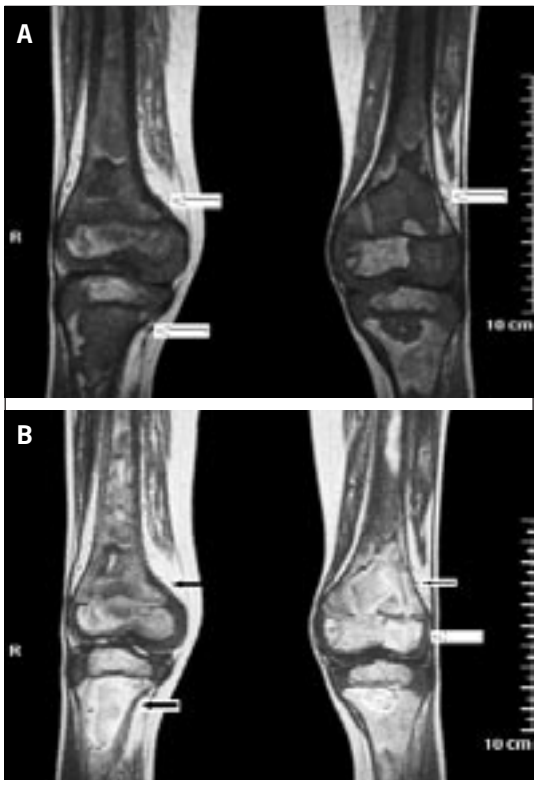

Figure 1. Osteonecrosis of medial femoral condyle and tibial plateau demonstrate low signal intensity on T1 weighted (A) and high signal intensity on T2 weighted images (B). Fracture of lateral femoral condyle and reactive marrow edema are also observed.

reduction of treatment-related morbidity. Osteonecrosis is a potentially disabling complication of cancer treatment[1]. Although osteonecrosis has been reported rarely in patients receiving high-dose methotrexate and doxorubicin, it is the most common complication related with high-dose corticosteroid administrations[2,8]. We thought that the development of osteonecrosis was strongly related to steroid administration because osteonecrosis occurred before high-dose methotrexate and after high-dose corticosteroid administration.

Age greatly influences the risk of osteonecrosis and older age is a known risk factor[5]. The maturing bone of adolescents may be more susceptible to the development of osteonecrosis. With epiphyseal closure, corticosteroid-induced marrow hypertrophy results in elevated intraosseous pressure followed by reduced intramedullary blood flow, marrow ischemia, and ultimately necrosis. In contrast, immature bone may buffer increased pressure at the epiphyseal plate[9]. Even though older children and adolescents are at highest risk for osteonecrosis, younger children are clearly not exempt from this toxicity, although their course may be transient and reversible. Mattano et al reported that the mean age of ALL patients with osteonecrosis was 13 years and among them only 0.9% were younger than nine years old[5]. Symptomatic osteonecrosis occurred in 1.1% of patients with childhood ALL enrolled in the AIEOP-ALL 95 study[6]. One of them was younger than five years old and this patient had congenital bilateral coxa vara. Strauss et al reported that five years, cumulative incidence of osteonecrosis among 187 patients was 7.3% and risk of osteonecrosis development for those aged 9-18 is five times greater than for those under the age of nine[4]. Burger et al reported the overall five-year cumulative incidence for osteonecrosis as 1.8%[10]. For the age group < 10 years, the incidence rate for developing osteonecrosis is 0.2%, and for patients older than 10 years it increases to 8.9%. Comparison of steroid doses and osteonecrosis development in different ALL trials is given in Table 1. In our patient osteonecrosis was diagnosed at the age of four and there was no additional skeletal anomaly. This is a rare condition. Development of osteonecrosis in the very young may be related to use of a very high-dose of prednisolone (total cumulative prednisolone dose was 9520 mg/m^2) in a short period. We think that if a conventional dose of prednisolone been administered instead of HDMP in the second remission induction protocol, osteonecrosis may not have developed. However, as we have no experience with other cases relapsing this quickly and since there were no cases in the literature who were readministered HDMP, this comment is no more than speculation.

Occurrence of osteonecrosis is generally seen 1-2 years after the beginning of ALL treatment. Arico et al reported that the median

Table 1. Comparison of steroid doses in different ALL trials

Trial	Age (year)	Prednisolone dose in mg/m^2	Incidence (%)
ALL-BFM 95	1-9	3411-6993	0.2
	10-18		8.9
	15-18		16.7
CCG-1882	1-9	7782-11150	0.9
	10-15		13.5
	16-20		18
DFCI, 87-01	0-18	7600-21240	6
DFCI, 91-01	0-18	7920-21530	9
AIEOP- ALL 95	0-5	1820-3008	0.3
	6-9		0.7
	10-17		7.4

period from diagnosis of ALL to development of osteonecrosis was 17 months (range 8-45 months)[6]. In the other two studies median time from diagnosis of ALL to development of osteonecrosis was reported as 14 and 30 months[3,4]. Mattano et al reported a patient who developed osteonecrosis after induction therapy[5]. In our patient osteonecrosis developed within five months after the beginning of chemotherapy. Similarly, the reason for the development of osteonecrosis in a very short time may be related to usage of a very high-dose of prednisolone in a short period.

Based on the results observed in our case, clinicians should be watchful for the development of osteonecrosis during use of high-dose steroid. Magnetic resonance should be obtained in suspected cases and, if necessary, treatment protocol should be modified.

REFERENCES

1. Murphy RG, Greenberg ML. Osteonecrosis in pediatric patients with acute lymphoblastic leukaemia. Cancer 1990;65:1717-21.
2. Wei SY, Esmail AN, Bunin N, Dormans JP. A vascular necrosis in children with acute lymphoblastic leukaemia. J Pediatr Orthop 2000;20:331-5.
3. Schroer WC. Current concepts on the pathogenesis of osteonecrosis of the femoral head. Orthop Review 1994;23:487-97.
4. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukaemia. J Clin Oncol 2001;19:3066-72.
5. Mattano LA Jr, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukaemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000; 18:3262-72.
6. Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukaemia. Haematologica 2003;88:747-53.
7. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison with conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic leukemia for long-term follow-up. Leukemia 2003; 17:328-33.
8. Marymont JV, Kaufman EE. Osteonecrosis of bone associated with combination chemotherapy without corticosteroids. Clin Orthop 1986;204:150-3.
9. Wang GJ, Sweet DE, Reger SI, Thompson RC. Fat-cell changes as a mechanism of avascular necrosis of the femoral head in cortisone treated rabbits. J Bone Joint Surg Am 1977;9:729-35.
10. Burger B, Beier R, Zimmermann M, et al. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)-experiences from trial ALL-BFM 95. Pediatr Blood Cancer 2004; [Epub ahead of print].

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