

Bilateral knee and right ankle osteonecrosis in an adolescent girl with acute lymphoblastic leukemia

Akut lenfoblastik lösemili adolesan bir kız çocukta her iki diz ve sağ topukta osteonekroz

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Abstract

Although rare, avascular necrosis of bone is a serious and incapacitating complication seen in children with acute lymphoblastic leukemia receiving high dose steroids. Here we present a 16 year-old girl who developed bilateral knee and right ankle avascular osteonecrosis one year after intensive chemotherapy for medium risk acute lymphoblastic leukemia. Indirect curettage of necrotic tissue and bone grafting were performed for both knees whereas conservative measures had been sufficient for the ankle. Early recognition of this condition is important in prevention of disabling sequela in skeletal system. (*Turk J Hematol 2009; 26: 34-7*)

Key words: Avascular osteonecrosis, acute lymphoblastic leukemia, child

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Özet

Yüksek doz steroid tedavisi alan akut lenfoblastik lösemili çocuklarda avasküler kemik nekrozu ender ancak ciddi ve sakatlık bırakan bir komplikasyondur. Orta risk akut lenfoblastik lösemi için yoğun kemoterapi alan ve her iki diz ve sağ topukta avasküler osteonekroz gelişen 16 yaşında bir kız hasta sunulmuştur. Her iki diz nekrotik dokunun küretajı ve kemik grefti ile tedavi edilirken, topukta konservatif tedavi yeterli olmuştur. İskelet sisteminde sekel bırakabilen bu durumun erken tanınması önemlidir. (*Turk J Hematol 2009; 26: 34-7*)

Anahtar kelimeler: Akut lenfoblastik lösemi, avasküler osteonekroz, çocukluk çağı

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Introduction

Avascular osteonecrosis (AON) is characterized by partial loss of the bone. It is often seen as a complication of long term use of high dose steroids in children with acute lymphoblastic leukemia (ALL), other malignant tumors and even in healthy children [1-3]. Its incidence varies between

1.09 % and 16 % in different series of children with ALL, though radiological incidence is even three times more common in asymptomatic children with ALL [3-8]. Clinical manifestations resemble those of leukemic infiltration of the bone. We here report a case of severe AON in both knees and right ankle occurring during maintenance chemotherapy in an adolescent girl with ALL.

Case

A 16 year-old girl was admitted with a three weeks history of fever, fatigue, pallor, generalized lymphadenopathy and bulky hepatosplenomegaly. She had pancytopenia (Hb: 8.2 g/dl, WBC: 1670/mm³, platelet count: 15200/mm³). Pre-B ALL was diagnosed (CD 10, 19, 22, 45, cyIgM, HLA-DR positive) with 97% blasts in the bone marrow. T (4; 11) and t (9; 22) by RT-PCR was negative. With ALL-BFM 95 treatment protocol prednisone good response and complete remission were observed on days 8 and 33 respectively. During remission induction, she had sinus aspergillosis which was successfully treated with liposomal amphotericin B for 4 weeks, followed by itraconazole for 3 weeks. She also developed vincristine neurotoxicity during itraconazole treatment that caused the discontinuation of itraconazole. Prophylactic ciprofloxacin was given during neutropenic periods. Two years after diagnosis while on maintenance therapy, she developed pain in both knees that forced a negative search for relapse. Intensity of bone pain gradually increased especially after long term standing and walking over the next 5 months. Two months after completion of maintenance chemotherapy, a magnetic resonance imaging (MRI) was performed due to acute hyperemia and swelling in both knees which showed diffuse medullar pathological signal in 1/3 distal femur and 1/3 proximal tibia, consistent with avascular osteonecrosis (Figure 1a, b). Arthroscopical examination of both knees revealed a wide osteochondritis dissecans of both medial femoral condyles however, articular cartilage was not completely separated. Indirect curettage of bony necrotic tissue (forage) and bone grafting were performed in both femoral condyles. Pathologic examination of resected specimen, confirmed the diagnosis of AON (Figure 2). Immediately after operation, passive motion exercises were started and weight bearing was not allowed for one month in order to provide graft healing. Six months later, she had severe pain in the right ankle due to another osteonecrotic focus in the medial section of talus (Figure 1c) which was treated with conservative measures including rest, avoidance of long and strenuous walks, refraining from weight gain. After two years off chemotherapy she is now well and could easily walk without limping only with a slight pain left in the right ankle.

Discussion

While late complications and impairment in quality of life due to chemotherapy have been largely studied, deleterious side effects of therapy on musculoskeletal system like pain, bone marrow edema, acute osteonecrosis, fractures, disability to move, deformation or loss of mineralization has encountered less attention [9]. Although the frequency and time of occurrence of these is not well identified the best reported is the incidence of AON being between 1.09% and 16% in different series of children with ALL and mostly occurring 3-5 years after diagnosis [3-8]. AON is more common in children over 10 years and in girls, largely in weight bearing joints however clinical features are extremely variable ranging from asymptomatic patients to limping. Our patient was an adolescent girl who

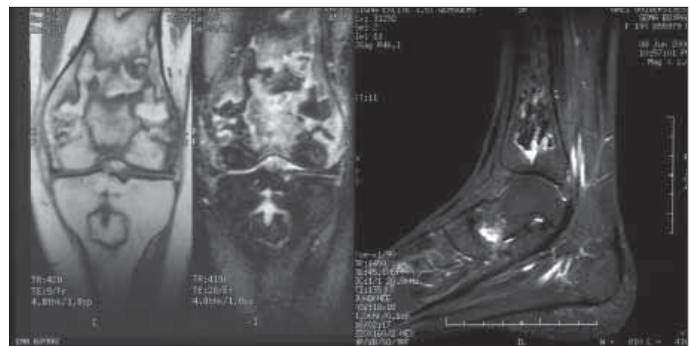


Figure 1. T1 (a) and T2 (b)-weighed images of the knee reveals geographism that is the decreased signal intensity on T1-weighted images (black arrows) and increased signal on T2-weighted images (white arrows) typical for acute osteonecrosis. Increased signal intensity with geographic pattern in the talar head and distal tibia (black arrows) in T2 weighed images of the ankle joint

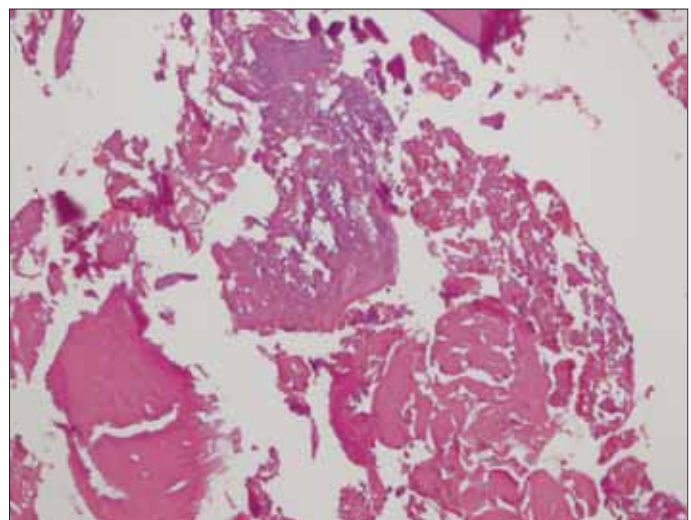


Figure 2. Bone marrow necrosis with associated osteonecrosis-tumor cells appearing as eosinophilic cell ghosts and empty lacunae in bony trabeculae with loss of osteocytes (Hematoxylin-eosin, x 200)

developed bilateral AON in both knees towards the end of maintenance chemotherapy and later in right talus. AON manifested itself initially as mild bone pain and tenderness over the involved areas and progressed rapidly to cause inability to walk. The time interval passed from the first mild pain to the severe incapacitating walking disability was only 5 months. Bone marrow and detailed radiological examinations should be done to distinguish leukemic relapse as clinical findings are similar. MRI is an easy and sensitive tool which recognizes AON by the characteristic low intensity signal demarcation consistent with bone infarction [9, 10]. It could also differentiate AON from leukemic relapse with 90 % accuracy with the later through multiple, well-defined nodular lesions [11].

Pathogenesis of AON is not well known. It seems to be a complex pathological process involving, suppression of osteoblasts, osteocyte apoptosis, and mechanical obstruction due to thromboembolism in sinusoidal vessels. When resorption of subchondral bone around necrotic area deteriorates the bony architecture, sustained pressure of the body weight and motion

lead to bone fracture and collapse of the adjacent articular cartilage [9]. Steroids have been shown to increase apoptosis in osteocytes and association of AON with prolonged administration along with high dose steroid therapy suggests that it may have a role in the development of this complication in children with ALL [3, 8, 9]. Comparing steroid doses in different ALL trials reveal that when total steroid dose is higher, bone morbidity like AON become more prevalent [3, 12]. Strauss et al also pointed out the potentially more toxicity of dexamethasone on the skeletal system compared to prednisone [12]. However there is evidence that shows steroids used as an anti-emetic agent in cancer patients can also cause AON [13]. Our patient was the only symptomatic case of AON among our 82 patients (25 of them were over 10 years of age) treated with the same ALL BFM-95 protocol which consists of 1837 mg/m² steroid as prednisone in induction, dexamethasone 236 mg/m² in reinduction, and 252 mg/m² during maintenance of leukemia therapy (total steroid dose 5091.96 mg/m² as prednisone; 1mg dexamethasone=6.67 mg prednisone). Despite high risk patients (n:15) received additional 1841.16 mg/m² steroid as prednisone, no symptomatic AON was observed within that group. Other chemotherapeutic drugs or antimicrobials like itraconazole which is known to inhibit the metabolism of corticosteroids might have increased the adverse effects of steroids on bone and therefore might have contributed to the pathogenesis of AON in our patient.

In selected high risk patients, prophylactic use of fluoroquinolones is suggested to reduce the incidence of Gram-negative bacteremias. Ciprofloxacin which has been the principal quinolone used in pediatrics has been reported to have musculoskeletal adverse effects like arthropathies [14, 15]. Although it causes cartilage damage in juvenile animal models and in necropsy materials of adults there is no evidence that it causes AON in children [15]. Furthermore, imaging and histopathological appearance of ciprofloxacin induced cartilage abnormalities is different from AON.

Susceptibility of AON in pediatric ALL could suggest a role for genetic discrepancy. Van Beek et al studied the role of lipid metabolism however no contribution to an increased risk of AON was found [16]. Although not found in a small number of patients [5] presence of MTHFR 677T allele might also be searched as a risk factor for AON in pediatric ALL like it was in sickle cell disease [17].

It is shown that, at the end of one year therapy containing high cumulative doses of steroids 15% of ALL patients even without any clinical symptoms have changes in MRI consistent with AON. Although most of these patients could complete the scheduled therapy without progressive joint damage, patients with severe pain and earlier changes in MRI might require modification of treatment [10]. In this regard, although some groups suggest routinely screening certain joints that are susceptible to AON under chemotherapy, timely performance of MRI for early diagnosis seems more feasible.

Early onset and severity of symptoms might determine both modification of causative drug therapy and alternatives of treatment to heal AON. Chollet et al replaced steroids by metho-

trexate in patients with ALL who had AON of the ankle and observed significant regression of the lesions [18]. However in another study in which interval between diagnosis of malignancy and AON was 16 months, therapy was not changed in any of the ALL patients with AON owing to completion of the steroid containing part of the treatment [19]. Our patient did not need any modification of chemotherapy since AON diagnosis was made after the chemotherapy was stopped.

Healing treatment options of AON are based on the severity of the disease. Asymptomatic patients might just be observed whereas children with pain need medical interventions such as limiting the physical activity, avoiding weight gain and using analgesic drugs. The multipotentiality of stem cells lead investigators to inject autologous marrow into the lesions which has been reported to have promising results like slowing the disease progression [9]. Other non-pharmacological procedures like electrical stimulation, hyperbaric oxygen, administration of low molecular weight heparin have also been encountered in small groups of patients being mostly ineffective in steroid related disease. Surgery is suggested only when conservative therapies fail. Our patient had surgical intervention for the knees however conservative treatment had been adequate for the ankle.

In conclusion, symptomatic AON, is an increasingly recognized side effect of intensive chemotherapy in childhood ALL and must be kept in mind when a patient develops bone pain. While dealing with leukemia, in the case of bone pain, the very first suspicion is the disease relapse which prompts the physician to search for it. Nevertheless, it is substantial to employ other diagnostic options in the case of no relapse especially when there are symptomatic joints. AON can be regarded as the invisible part of iceberg since the incidence of asymptomatic cases is much higher than symptomatic ones.

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