Delayed diagnosis of acute leukemia in a patient with bone pain and fracture

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In childhood acute lymphoblastic leukemia (ALL), non-hematological manifestations involving the musculoskeletal system can also be encountered. These manifestations may cause a delay in the diagnosis of leukemia. The presented case in this report is a six-year-old boy who developed bone pain and long bone fracture and was diagnosed as ALL after a considerable delay. This case is presented to draw attention to the fact that leukemia must be considered in pediatric patients who present with bone manifestations.

Key words: children, leukemia, bone involvement.

The most common childhood cancer is acute lymphoblastic leukemia (ALL), accounting for about 33% of all pediatric malignancies[1]. Common clinical presentations of leukemia include anorexia, fatigue, fever, pallor, purpura, hepatosplenomegaly, lymphadenopathy, anemia, neutropenia, lymphocytosis, and thrombocytopenia[2,3]. These symptoms are frequently accompanied by musculoskeletal signs, such as limping, joint and bone pain[4] and radiographic abnormalities, at presentation. However, it is a fact that the diagnosis of patients with leukemia who present with mainly musculoskeletal findings may be considerably delayed due to the work-up of these symptoms, which are also within the scope of orthopedics and physiotherapists.

Bone fracture, as a presenting symptom of childhood ALL, has been reported at diagnosis, and during and following treatment, with incidence rates ranging from 10% to 40%[5]. Fractures mostly involve the spine, associated with osteoporosis, with occasional peripheral locations[2]. Herein, we report a six-year-old boy with ALL whose diagnosis was delayed as long as two months because the presenting symptoms were bone pain and long bone fracture.

Case Report

A six-year-old boy with diffuse bone pain, coexistent fracture of the left distal radius and inability to walk was referred to our hospital because of malaise and pallor. It was learned that the diffuse, continuous bone pain, which was not disabling, had started two months before and increased progressively. A few weeks after its initiation, a fissure on his right elbow developed after a minimal trauma due to a fall while walking and a plaster cast was applied. One month later, a transverse fracture (Fig. 1) occurred on his left forearm due to another mild trauma, which was followed soon thereafter by fatigue and limping. He was admitted to a physiotherapist at the start of his bone pain and an orthopedist twice when he developed the fissure and bone fracture. He was referred to a pediatrician after the development of malaise, pallor and inability to walk. Personal and family medical histories were unremarkable.

His weight was 18 kg (10-25p), height 110 cm (10-25p) and body temperature 36.3°C. He had disseminated bone pain and a plaster cast on his left forearm. His liver extended 1 cm below the right costal margin at the midclavicular line; his remaining systemic examination was normal.

His hemoglobin was 97 g/L (9.7 g/dl), white blood cells $3.2x10^9$/L ($3200/mm^3$), platelets $244x10^9$/L ($244,000/mm^3$), mean corpuscular volume (MCV) 87 fl, lactate dehydrogenase 147 U/L (N: 155-280), calcium 8.9 mg/dl (N: 9-10.1), phosphorus 4.9 mg/dl (N: 3.1-5.9), alkaline phosphatase 110 U/L (N: 218-499), parathyroid hormone (PTH) 42.60 pg/ml (N: 10-65), 25-(OH) vitamin D 21 ng/ml (10-40), and osteocalcin 34.30 ng/ml (N: 14-42), with normal liver and renal function tests. His peripheral blood and bone marrow smears revealed 60% and 80% lymphoblasts, respectively. Flow cytometric analysis was reported as pre B ALL with CD10 84%, CD19 83%, CD10+CD19 82%, CD22 50%, cCD22 50%, CD24 94%, CD34 40%, cCD79 68%, HLADR 78%, sIGM 99%, cμ 99%, TDT 23%, and CD45 24%. Karyotyping examination of bone marrow revealed normal findings as 46, XY and negativity for t(9;22), t(4;11), t(8;11), 11q23 MLL. There was no central nervous system involvement. Radiograph of the bones revealed diffuse osteopenia, lytic lesions and a transverse fracture on the left distal radius as seen in Figure 1. Bone mineral densitometry showed L1-L4 Z score as -1.7.

Turkish-BFM ALL (medium risk) therapy was started. His plaster cast was renewed. Endocrinologic laboratory work-up relevant to the etiology of bone fracture revealed no definite pathology. 400 U vitamin D and 500 mg calcium peroral (p.o.) were started. As his folic acid level was below the normal range, folic acid replacement therapy (1 mg p.o.) was also started.

During his induction chemotherapy, he developed limping. His neurological examination, lumbosacral magnetic resonance imaging and direct X-rays of pelvis and legs, and cerebrospinal fluid were all normal. His limping resolved spontaneously after consolidation chemotherapy. Folic acid replacement therapy was also stopped after three months. At present, he is in remission and on maintenance chemotherapy without any symptoms, including no musculoskeletal symptoms.

Discussion

Acute lymphoblastic leukemia (ALL) may cause alterations in bone metabolism and defective mineralization. Leukemic infiltration and expansion of the bone marrow spaces leading to destruction of spongiosa, as well as the factors secreted by the leukemic cells, such as osteoblast inhibiting factor and PTH-related peptide, might contribute to bone loss in ALL[6]. Additionally, local hemorrhage and osteonecrosis of the adjacent bone give rise to osteolytic lesions[2]. In addition to the disease process, corticosteroids and other types of therapies might contribute to bone morbidity[7]. Skeletal morbidity, which is characterized by bone pain, osteonecrosis, fractures, loss of mobility, bone deformation, or osteopenia, is frequently encountered in patients with ALL at diagnosis, during chemotherapy and thereafter[5].

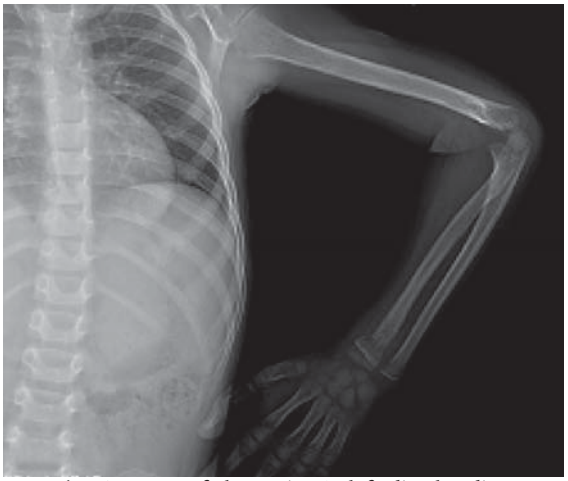

Fig. 1. X-ray of the patient's left distal radius.

In our patient, bone pain and long bone fissure and fracture preceded nonspecific signs of leukemia like pallor. Osteopenia and osteolytic lesions were the other skeletal pathologies. Bone fractures are rare features of childhood leukemia, seen in 5.7-12%[8] of ALL patients and being even rarer in acute myeloid leukemia[9]. Fractures were reported to be localized mostly in the spine, associated with osteoporosis, and occasionally in peripheral locations[2], and after minimal or moderate trauma[5]. In our patient, both the fissure on the right elbow and the fracture on the left forearm developed after mild traumas. However, bone pain is a frequent phenomenon in children with ALL, mostly involving long bones and vertebral bodies, due mainly to osteoporosis and compression fractures. The pain may be intermittent, localized, sharp, severe, and

sudden in onset[2]. In our patient, the bone pain was diffuse in all bones, continuous and mild, although its intensity increased progressively. Neither bone pain nor long bone fissure/fracture in the current case was associated with osteoporosis. It should always be kept in mind that none of the radiologic abnormalities like osteopenia, lytic lesions, radiolucent metaphyseal bands, compression fractures, and isolated periosteal reactions, which are encountered in the majority (41-75%)[1,2], is pathognomonic for leukemia[2]. A lucent metaphyseal band, on radiologic examination, which was considered as a specific finding of leukemia, was suggested to be less common than had been reported previously, making it a less reliable diagnostic sign[4]. Hence, the most common radiological abnormality in ALL is osteopenia (16-41%) (10% at diagnosis), which is also nonspecific, since it may also be due to various reasons like malnutrition and drugs (steroids and chemotherapy). Lytic lesions are especially localized in the metaphysis of long bones but may occur in flat or small bones as well. They may be associated with periosteal reaction[2]. On the other hand, a poor correlation exists between the symptoms and the radiologic lesions. Many cases of ALL who display radiologic bony manifestations are associated with a favorable prognosis[10]. Our patient's symptoms like diffuse bone pain and limping resolved spontaneously with consolidation chemotherapy, when the leukemia was controlled, in accordance with the literature[1].

Musculoskeletal symptoms were reported in 38.3% of patients with ALL at presentation[2,11] and 21% presented only with musculoskeletal symptoms[1]. Patients with no blasts in peripheral blood are misdiagnosed as juvenile rheumatoid arthritis (JRA), septic arthritis, osteomyelitis or diskitis, resulting in a delay in the correct diagnosis and appropriate treatment[1,4]. To distinguish JRA from ALL, Jones et al.[12] reported that peripheral blood smear abnormalities, especially a low-normal platelet count and low leukocyte count, along with presence of nighttime pain are the most sensitive and specific factors. Longer duration of symptoms before diagnosis was reported to reduce the survival rate[4]. Delay of diagnosis in our patient was two months since he was admitted to a physiotherapist when his bone pain had started and to an orthopedist following fissure development. It was after the development of the bone fracture that he was admitted to a pediatrician, at which point he had developed concurrent nonspecific signs of leukemia.

This case, who is on maintenance therapy without any musculoskeletal or other complaints, is presented to draw attention to the fact that acute leukemia should always be considered in the differential diagnosis of children who present with musculoskeletal signs and symptoms like marked osteopenia, bone pain and fractures[3]. Especially bone and joint complaints with severe nighttime pain and mild to moderate complete blood count changes should be kept in mind for pointing to leukemia as the underlying cause[12].

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