Femoral bone relapse in adult acute lymphoblastic leukemia Philadelphia chromosome positive: a case report

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ABSTRACT

We present a case of a 39-year-old male patient diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who relapse in unusual extramedullary site like bone. The patient was admitted complaining of intense pain in the left thigh 1 year following complete remission. Magnetic resonance imaging (MRI) revealed abnormal multifocal involvement in the left femur suggested malignancy. Bone marrow aspiration indicated recurrence of leukemic cells. These findings suggested bone relapse occurred simultaneously with medullary relapse.

Keywords: acute lymphoblastic leukemia, Philadelphia chromosome, bone relapse

INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents the most common form of childhood leukemia and, by contrast, only 20% of all leukemias among adults. (1) ALL carries a poor prognosis in adults with a curability rate around 30% at 5 years. (2)The presence of the Ph chromosome is, in itself, considered one of the worst prognostic factors in ALL. Unfortunately most patients develop reccurent disease within the first 12-24 months of achieving their first remission. The most frequent sites of isolated extramedullary relapse tend to be in the „sanctuary sites" of the central nervous system (CNS) and testes. Rarely, extramedullary relapse has been reported in the ovary, breast, eye, bone, and kidneys. We present a case of early bone relapse in adult patient with Ph^+ ALLsimultaneously with medullary relapse.

CASE REPORT

An Iranian 39-year-old man was admitted in December 2010 with a one week history of worsening abdominal pain, fatigue, weight loss, sweats. On examination he had pallor, bilateral axillar lymph nodes 4 cm diameter, hepato-splenomegaly, no sign neurological and testicular examination normal. Hemogram revealed anemia (Hb – 8.7 g/dl), thrombocytopenia (PLT –72,000/mm^3) and a very high leucocyte count (WBC – 300,000/mm^3). Bone marrow examination showed 74% immature cellsmorphological classified as lymphoblasts L1 acording to the FAB (French-American-British) classification – Figure 1. Immunophenotyping of blast cellsidentified: CD19+, CD 79a +, CD3-, TdT+, CD10+, cμ -, sIg -, cy Ig -. These features were consistent with the diagnosis of common ALL, EGIL B2according to the EGIL classification (European

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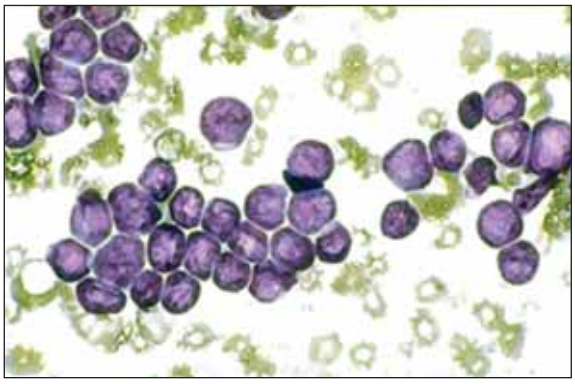

FIGURE 1. *Bone marrow showing small cells with scant cytoplasm, condensed nuclear chromatin and indistinct nucleoli*

Group for the Immunological Characterization of Leukemias). (3) Cytogenetic analysis by fluorescent in situ hybridisation (FISH) identified the abnormal translocation t(9;22) – the Philadelphia chromosome – in more than 90% of the nuclei analyzed. A molecular evaluation by PCR (polymerase chain reaction) found fusion BCR-ABL protein, p210 variant, with increase tyrosine-kinase activity. Patient was treated with UKALL treatment protocol in adult ALL adding TKI (inhibitors tyrosine-kinase), therapy target for Philadelphia chromosome. After induction treatment observed a rapid favorable evolution with regression of symptoms onset, absence of hepatosplenomegaly, normal hemogram, bone marrow remission (< 5% blast cells), partial cytogenetic response (< 35% Ph+ metaphases). A evaluation molecular was not performed. It was continued consolidation therapy and was initiated a search procedure an unrelated donor for allogeneic stem cell transplantation (there is no related donor). This good response is maintained until January 2012 when the patient presents to the hospital with intense pain in the lower third of the left thigh occurred 24 hours before. Local clinical examination revealed no swelling, warmth or changes in skin color andwithout any bone pain. Laboratory studies describe changes in blood counts:recurrence of thrombocytopenia (PLT – 45.000/mm^3), anemia (Hb – 10.8 g/dl) and total leukocyte count (WBC – 8.100/mm^3). No blast cells on peripheral blood smears. Bone marrow aspiration revealed relapse: 18% blast cells with the same morphology and immunophenotype as the onset of the disease. Femoral bone radiography showed a normal radiologic.Venous Doppler ultrasound showed no signs of thrombosis of the lower limbs painfully. A magnetic resonance imaging (MRI) was performed on the left femur. Examination describes in the middle third of the left femur an irregular area about 15/17mm in the axial plane and 30mm in craniocaudal direction with hypersignal T2 and STIR, hypodense T1 with annular peripheral gonadofilie, stretched perilesional edema in the soft tissues adjacent extended, without interrupting the cortical bone. (Figures 2, 3, 4) Imaging description suggests infiltration femoral with leukemic infiltrate compatible aspect. Further investigations have not been carried out because the patient decided to return to his homeland and so the pacient was lost track of our clinic.

DISCUSSION

Most patients with ALL, unfortunately, develop recurrent disease within the first 12-24 months of achieving their first remission, at a time when they are still receiving maintenance

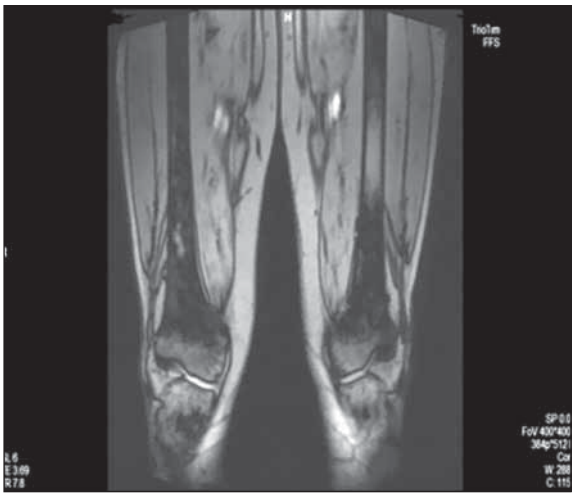

FIGURE 2. *Magnetic resonance image describes infiltrative processes in the middle third of the left femur suggested malignancy*

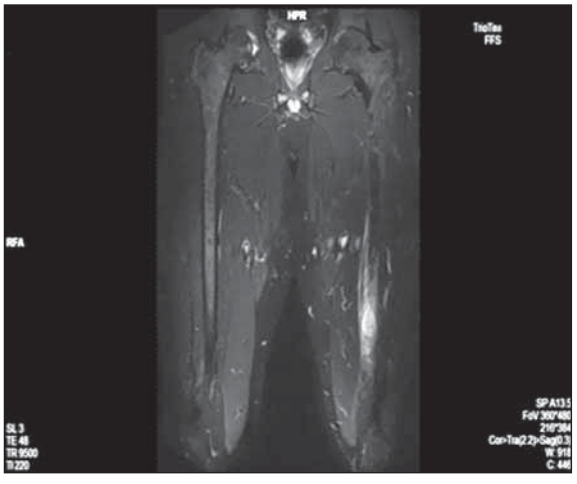

FIGURE 3. *Magnetic resonance image describes infiltrative processes in the middle third of the left femur suggested malignancy*

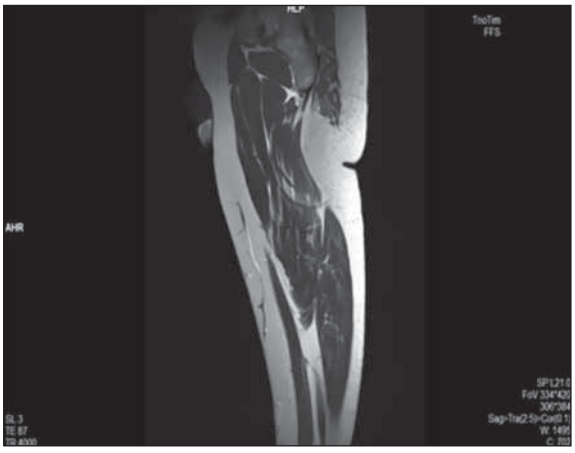

FIGURE 4. *Magnetic resonance image describes infiltrative processes in the middle third of the left femur suggested malignancy*

chemotherapy. The most site of relapse is the bone marrow, CNS and/or testes. Data on extramedullary relapses of ALL is limited in the adult population. The majority of the literature is in pediatric patients or in the postallogeneic hematopoietic stem cell transplantation setting. Extramedullary relapse in unusual sites like eye, kidney, ovaries and bone have been reported in long-term survivors of ALL. Our patient had bone femur involvement, but he also had relapsed disease in bone marrow. Pathological features at onset (age, leucocyte count, presence of chromosome Philadelphia) classified patient in a high risk group and predicted relapse. Both age and initial WBC count have istorically been considered clinically significant prognostic factors in the management of adult patients with ALL. Early prospective multicenter studies demonstrated that older age (> 35 years) and higher initial WBC count (30 x 10^9/L) were significantly predictive of decreased remission duration. Philadelphia-chromosome is the most common cytogenetic abnormality among adults (25%) and relatively uncommon among childhood (3%). (4) The 5-years OS rate among patients with Ph-positive and Ph-negative disease was 25% vs 41%. (5) Philadelphia-chromosome positive disease carries a very poor prognosis, and long-term survival, even with high-dose chemotherapy, is rare.The prevalence of Ph+ ALL increases with age an is usually linked with a higher WBC, two factors considered to be associated with worse prognosis in and of themselves. (6) The development of imatinib, a tyrosine kinase inhibitor with relative specificity for BCR-ABL, has dramatically changed the treatment and outcome of patients with Ph+ ALL. Thus, for patients with Ph+ disease, allogeneic transplant in first complete remission is commonly recommended and may be curative in a minority of patients. (7) Is there any prognostic significance between p210 and p190 molecular abnormalities in adults with Philadelphia chromosome-positive acute leukemia? More studies suggests that the disease process in Ph-positive acute leukemia is not influenced by the different molecular abnormalities (p190 versusp210) and are not identifysignificant associations between the molecular abnormalities and patient age, leukocyte count, or FABtype. (8) The pathophysiology of extramedullary relapse at unusual site is unknown. The fact that most patients with bone relapses have had prior and / or subsequent bone marrow or CNS relapse indicates that there may be persistence of resistant leukemic clones. Preliminary research suggests thatextramedullary involvement may, in part, originate from leukemic cells in the bone marrow, even if those cells are not detected using conventional morphologic assessment. These subclinical levels of residual leukemia are termed minimal residual disease (MRD) and can be evaluated using more sensitive assays: flow cytometry or polymerase chain reaction (PCR).In one retrospective study, submicroscopic bone marrow involvement was detected via real-time quantitative PCRin the majority of pediatric ALL patients who were thought to have isolated extramedullary disease. (9) Extramedullary relapse of ALL to the femur is rare and has primarily been reported in the pediatric literature. Our patient had increasing bone lesions while the recurrence of disease in bone marrow. The prognosis of relapsed ALL in adults is poor.

CONCLUSION

Extramedullary relapse in unusual sites like eye, kidney, ovaries and bone have been reported in long-term survivors of ALL. Rare cases of isolated bone relapse have been documented in pediatric literature, the majority have been late relapses (the mean time from diagnosis being 6.3 years). (10) In the adult patient population with ALL, extramedullary relapse has been predominately reported in the postallogeneic stem cell transplantation setting. The particularity of the presented cases consist in abone relapse simultaneously with the bone marrow relapse (at 1 year from diagnosis). More adverse prognostic factors (age, higher WBC count, presence of Philadelphia chromosome,persistence of MRD) may be responsible for early marrow relapse and atypical localization of leukemic clones.

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