A Case of Avascular Necrosis of the Femoral Head as Initial Presentation of Chronic Myelogenous Leukemia

Ji Yong Moon, M.D., Byung Su Kim, M.D.,2, Hye Ryeon Yun, M.D., Jung Hye Choi, M.D., Young Yul Lee, M.D., In Soon Kim, M.D. and Myung Ju Ahn, M.D.

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea; Armed Forces Capital Hospital2, Sungnam, Korea

INTRODUCTION

Chronic myelogenous leukemia (CML) is a malignant clonal disorder of hemopoietic stem cells characterized by abnormal proliferation and accumulation of immature granulocyte. Leukostasis is one of the complications of CML and is characterized by partial or total occlusion of microcirculation by aggregation of leukemic cells and thrombi leading to respiratory, ophthalmic or neurologic symptoms. We experienced a rare case of avascular necrosis of the femoral head as the initial presentation of chronic myelogenous leukemia. A 24-year-old male patient was admitted to our hospital with pain in the right hip joint. The patient was diagnosed to be suffering from chronic myelogenous leukemia by packed marrow with granulocytic and megakaryocytic hyperplasia and the presence of Philadelphia chromosome. The right hip joint pain was attributed to avascular necrosis of the femoral head. And the avascular necrosis could be considered as the complication of chronic myelogenous leukemia due to microcirculatory obstruction of the femoral head. The avascular necrosis of the right femoral head was treated with bipolar hemiarthroplasty.

Key Words : Femur Head, Osteonecrosis; Leukostasis; Leukemia, Myeloid, Chronic

CASE REPORT

A 21-year-old male patient was presented with pain in the right hip joint for 2 months. He was a soldier and went to the dispensary of the unit that he belonged to. He was referred to
The patient suffered from weight loss, mild dyspnea, fatigue, intermittent fever, and night sweat. The further history was uneventful. Upon physical examination, it was observed that the patient was in poor general condition with pallor skin and anemic conjunctiva. There were no signs of hemorrhagic diathesis or icterus. The spleen was palpable below the umbilicus and had a firm consistency. Cervical and inguinal lymph nodes were palpable. Heart and lungs were without any pathologic findings. The chest X-ray and electrocardiography were normal.

Laboratory investigations revealed leukocytosis with leukocyte count of 96,800/mm³, increased platelets with a count of 684,000/mm³, and hemoglobin level of 10.4 g/dL. The peripheral blood smear revealed 1% blast cells. Microbiology findings were sterile cultures of blood and urines.

Bone marrow examination revealed that the entire marrow space was packed with granulocytes and megakaryocytes. The bone marrow biopsy showed marked hypercellularity and the estimated cellularity was near 100%. The bone marrow aspiration showed 0.4% myeloblasts, 6% promyelocytes, 13.2% myelocytes, 15.2% metamyelocytes, 14.7% band neutrophils, 40% segmented neutrophils, 2.7% eosinophils, 0% basophils, 0.8% monocytes, 0.4% pronormoblasts, 0% lymphoblasts, 0% immature lymphocytes, 0.4% lymphocytes, 0.4% plasma cells, and 0% histiocytes suggesting chronic phase of CML. Chromosomal analysis of bone marrow revealed Philadelphia chromosome, t (9;22) and molecular cytogenetics also showed bcr-abl positive.

Treatment with hydroxyurea was induced, combined with immediate evaluation of right hip joint pain. Radiolucency superimposing the right femoral head was seen on the pelvic X-ray (Figure 1). Whole body bone scan showed increased uptake of the right hip joint. Magnetic resonance imaging (MRI) of both the hips revealed inhomogenously decreased signal intensity in the both proximal femur and acetabulum on T1 weighted images. (A) The left picture shows inhomogenously decreased signal intensity in the both proximal femur and acetabulum on T1 weighted images. (B) In the right picture, the outer areas of these areas had increased signal densities on T2 weighted images.
Intensity in both proximal femur and acetabulum on T1 weighted images. The outer areas surrounding these areas had increased signal densities on T2 weighted images (Figure 2). On application of contrast medium, area with former decreased signal density on the cranial part of the right femoral head and some smaller areas of the left femoral head, showed a lack of signal enhancement. Bilateral joint effusion, worse in the right than the left, was also seen. All together, MRI showed signs of necrosis of both the femoral heads.

The leukocyte count decreased from 96,800/ul to 26,300/mm$^3$ with the treatment of hydroxyurea (3 g/day) for 2 weeks and subsequently hydroxyurea was replaced with imatinib mesylate. With this treatment leukocytes were reduced from 96,800/mm$^3$ to 8,900/mm$^3$ within 3 weeks. The size of the spleen decreased to 3 cm below the costal margin within 1 month.

Following normalization of the peripheral blood counts, the patient was transferred to the department of Orthopedics. He underwent a bipolar hemiarthroplasty of the right hip joint, because the necrosis of the right hip joint was more severe than the left and he had no pain in the left hip joint. The postoperative course was complicated due to bleeding from the operative site possibly due to thrombocytopenia which may have been induced by imatinib mesylate. Temporarily, the medication of imatinib mesylate was stopped, and the patient was transfused with platelets and packed red cells. The biopsy revealed focal subchondral necrotic areas in the right hip joint (Figure 3).

The patient was on a continuous follow up and showed no complications with complete cytogenetic response and has been on medication of imatinib mesylate (400 mg/day).

**DISCUSSION**

CML is characterized by a chronic phase which lasts from months to years, and is followed by accelerated myeloproliferative phase and subsequently blast crisis. In the chronic phase, manifestations include anemia, splenomegaly, bleeding, and constitutional symptoms such as fatigue, lethargy, weight loss, or low-grade fever. As in the present case study our case of a 21-year-old male, symptoms secondary to leukostasis may also be the presenting features.

Leukostasis is defined as a pathological entity. Since there are no reliable clinical criteria, in practice, leukostasis is empirically diagnosed when patients present with leukemia, hyperleukocytosis and respiratory or neurologic distress. However, some patients have clinically suspected or pathologically proven leukostasis with leukemic blast counts significantly lower than 100,000/mm$^3$.

The biological mechanism underlying development and progression of leukostasis still remains unclear. Litchmann proposed a pathophysiological model of leukostasis, based on the rheological consequences of hyperleukocytosis. He determined that the viscosity of leukocyte suspensions in vitro increased dramatically when the fractional volume of leukocytes (also known as leukocrit) exceeded 12–15 mL/dL. The concentration of leukocytes necessary to produce such leukocrits is a function of the mean cell volume (MCV) of the cells. Since leukemic myeloblasts have larger MCV than leukemic lymphoblasts, leukostasis is more frequently observed in patients with acute or chronic myelogenous leukemia than in patients with acute or chronic lymphoblastic leukemia. However, leukemic blast concentrations necessary to reach leukocrit of 12–15 mL/dL are rarely seen. Therefore, additional factors possibly related to the adhesive or invasive properties of leukemic blasts, may be more important. There are indications that leukemic blasts-endothelial cell interactions may be triggered by locally released chemoattractant factors. Complement-induced granulocyte aggregation is a well documented mechanism of...
leukostasis). Several adhesion molecules (CD54, CD62E, CD62P, CD106) are up-regulated in endothelial cell of AML patients with leukostasis. Blasts appear to have the ability to secrete cytokines such as TNF-α and interleukin-1β and therefore bring about the activation of endothelium. For instance, activation of vascular endothelium by tumor necrosis factor-alpha (TNF-α) has been reported to increase the adhesion of myeloid blasts.

Once leukostasis is developed, signs and symptoms are usually related to the involvement of the respiratory or central nervous system. Additional but less common clinical findings include neck vein distension, gallop rhythm and electrocardiographic sign of right ventricular overload, myocardial ischemia, priapism, acute limb ischemia, bowel infarctions, renal vein thrombosis, sudden bilateral deafness and avascular necrosis of bone. Until now, in CML, avascular necrosis of femoral head due to leukostasis has not been adequately documented, probably due to the rarity of its occurrence. After reviewing the world medical literature, we encountered only few cases of CML associated with avascular necrosis of femoral head.

The current standard of care for hyperleukocytosis and leukostasis should be the immediate initiation of intravenous fluids, allopurinol, hydroxyurea and the correction of coagulopathy. Due to paucity of data on the efficacy of leukapheresis in reducing early mortality and/or improving overall survival, leukapheresis cannot be recommended as routine therapy. Unfortunately there are no evidences to prove that any of these measures have produced a reduction in the number of early deaths.

A variety of traumatic and nontraumatic factors contribute to the etiology of avascular necrosis. In adult patients, corticosteroid use and excessive alcohol intake are reported to account for more than 90 percent of cases. Additionally, other causes of avascular necrosis are systemic lupus erythematus, antiphospholipid antibody, trauma, sickle cell hemoglobinopathies, Gaucher's disease, Caisson disease (dysbarism), transplanta tion, interferon-α, inherited thrombophilia, or HIV infection. Avascular necrosis usually occurs in the anterolateral femoral head, although it may also affect the humeral head, femoral condyles, proximal tibia, vertebrae, and small bones of the hand and foot. Many patients have bilateral involvement at the time of diagnosis, including disease of the hips, knees, and shoulders. The goal of therapy for avascular necrosis is to preserve the naive joint for as long as possible. However, the optimal treatment has yet to be determined.

REFERENCES


18) Miller KD, Masur H, Jones EC, Joe GO, Rick ME, Kelly GG, Mican JM, Liu S, Gerber LH, Blackwelder WC, Falloon J, Davie RT, Polis MA, Walker RE, Lane HC, Kovacs JA. High prevalence of