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Case Report

Avascular necrosis of femoral head: a rare case as a symptom of the chronic phase in adult chronic myelogenous leukemia patients on nilotinib therapy

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ABSTRACT

Chronic myelogenous leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells characterized by abnormal proliferation and accumulation of immature granulocytes. Avascular necrosis (AVN) is a rare case in CML patients where a systematic review reported only 21 cases from 1984 to 2021 of which 17 cases were AVN of the femoral head (AVNFH) and 3 cases were associated with treatment with tyrosine kinase inhibitors, namely imatinib, desatinib and nilotinib. We report a 51-year-old male patient with complaints of hip joint pain. The patient was diagnosed with CML from bone marrow examination with hypercellular results and PCR examination which detected the presence of BCR-ABL transcription in the form of b2a2 fusion. The patient received nilotinib 200 mg every 12 hours. The diagnosis of AVN was established from clinical symptoms and radiological examination. The patient was planned to undergo a total hip replacement.

Keywords: AVN of femoral head, CML, Nilotinib

INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal malignant disorder of hematopoietic stem cells characterized by abnormal proliferation and accumulation of immature granulocytes.[1] CML is associated with at (9;22) translocation on the Philadelphia chromosome. CML often occurs in adults with an age range of 50 years.[2] CML is divided into several phases, namely the chronic phase, the accelerated phase and the blastic crisis phase.[3] CML begins with a chronic phase lasting 3-5 years which can continue into an accelerated phase and a blastic phase, which is generally fatal.[4] Leukostasis is a complication of CML and is characterized by partial or total occlusion of the microcirculation with aggregation of leukemic cells and thrombus thereby triggering respiratory, ophthalmic or neurological symptoms.[1,2]

Bone involvement in chronic myeloid leukemia (CML) occurs in 3-5% of cases. Skeletal abnormalities developing during the chronic phase of CML are associated with an ectopic process of myeloid metaplasia. AVN of bone is a rare osseous manifestation of leukaemia. AVN usually occurs in 0.12-10% of lymphoma and acute leukemia (especially acute lymphoblastic leukemia) especially after treatment with corticosteroids or radiotherapy.[5,6] Bone AVN occurs in areas with low collateral circulation. The most common areas to experience AVN are the head of the femur, head of the humerus, femoral condyles and tibial plateau.[7] AVN occurs as a complication of trauma or non-trauma. Most AVN cases occur as a result of non-trauma such as excessive use of corticosteroids and alcohol consumption. Other non-traumatic conditions that can trigger AVN are coagulopathy, hemoglobinopathy (sickle cell disease), chronic liver disease, gout, idiopathic hyperlipidemia, metabolic bone disorders, pregnancy, radiation, chemotherapy, smoking, systemic lupus erythematosus.[8] Coagulopathy can occur secondarily as a result from extravascular compression such as marrow fat enlargement, vascular wall disorders (such as

chemotherapy, radiation), or thromboembolic events. Ischemic conditions can cause subchondral infarction of the bone.[4,8]

A systematic review by Al-Mashdali et al which collected 18 scientific articles from 1984 to 2021 stated that there were 21 cases of AVN in CML patients of which 17 cases with AVN of the femoral head (AVNFH) and 4 cases with osteonecrosis of the jaw (ONJ).[9] A total of 5 patients with AVNFH were associated with interferon alpha therapy and 3 AVNFH patients who received tyrosine kinase inhibitors (TKI) for CML. One patient was found to have AVN after receiving nilotinib therapy for 9 months.[9] Cases of AVN in CML patients have been reported so rarely that we report the case of an adult male with CML manifesting as AVN of the femoral head (AVNFH).

CASE REPORT

The patient is a 51-year-old man who was hospitalized for the first time at the Sanjiwani hospital with complaints of fever since 3 days before entering the hospital. The patient also complained of nausea and vomiting and headache. The patient complained of pain in the groin since the previous 20 days. On the second day of hospitalization the patient complained of pain in the right upper abdomen. The patient complained of pain in the groin getting worse. The patient had no history of chronic disease and long-term drug consumption. The patient works as a farmer and lives in the village. The patient does not smoke but the patient's child is an active smoker. The patient has no family history of cancer. Patients often use pesticides in the fields and lift heavy weights while working.

The patient's blood pressure is 120/70 mmHg, pulse is 84 x/minute, temperature is 39.7^0 C and the patient's respiratory rate is 22 x/minute. On physical examination, the sclerae were not icteric and the conjunctiva was anemic. No enlarged lymph nodes in the neck area. Chest examination found vesicular breath sounds, no wheezing and crackles. The left heart border is normal and the heart sounds are normal S1 and S2, no murmurs or gallops. On the abdomen found a positive Murphy's sign. The liver is palpable 3 fingers below the costal arc and 3 fingers below the xiphoid process. There is enlargement of the spleen. Normal bowel sounds. The extremities were warm and there was no pitting edema in the pre-tibia.

A complete blood count obtained hemoglobin 9.0 gr/dL, leukocytes 23,280/uL, platelets 273,000/uL, MCV 86.8 fL, MCH 28.5 pg, neutrophils 20.49/88%, lymphocytes 2.09/9%, monocytes 0.47/2.1%, eosinophils 0.06/0.2%, and Basophils 0.17/0.7%. Renal function tests included urea 102 mg/dL and creatinine 1.22 mg/dL. Examination of liver function AST 41 U/L and ALT 50 U/L. Examination of electrolytes sodium 136 mmol/l, potassium 41 mmol/l and chloride 103 mmol/l. Negative HBsAg test. Examination of total bilirubin 1.2 mg/dL with direct bilirubin 0.1 mg/dL and indirect bilirubin 0.7 mg/d. After second day of hospitalization, a complete blood count was again carried out because the anemic condition appeared to be more severe and the results obtained were as follows: lymphocytes 2.3/8.7%, monocytes 1.02/3.9%, eosinophils 0.09/0.3%, and basophils 0.12/0.4%. Several tests were carried out to find out the source of infection such as urine examination, chest x-ray and abdominal ultrasound. Examination of urine and chest x-ray showed normal results. Abdominal ultrasound was performed to determine the possibility of cholelithiasis but results showed hepatosplenomegaly with an enlarged liver measuring 14.67 cm and an enlarged spleen measuring 13.86 cm. The patient was diagnosed with suspected cholecystitis due to a positive Murphy sign so empirical antibiotic therapy was given, namely sefoperazone sulbactam 1 gram every 12 hours.

Complaints of pain in the groin were felt to be getting worse so that a lumbosacral CT scan was performed to confirm the diagnosis and examination showed paralumbar muscle spasm and no compression or lithiasis was seen. The patient received a transfusion of 5 PRC bags and then had a complete blood count again with the results of hemoglobin 9.8 gr/dL, leukocytes 119.93/uL, platelets 1,123,000/uL, MCV 86.0 fL, MCH 28.0 pg, neutrophils 105.81/88.3%, lymphocytes 10, 58/8%, monocytes 1.89/1.5%, eosinophils 1.47/1.2%, and Basophils 0.18/0.1%. After 7 days of antibiotic therapy, a complete blood count was carried out with persistent leukocytosis results so that blood culture examination was continued with sterile results. The patient was referred for bone marrow examination with a temporary assessment of suspected CML.

Furthermore, the patient underwent examination of peripheral blood smears and examination of bone marrow aspiration. The results of peripheral blood examination were normochromic anemia with hyperleukocytosis dominantly neutrophilia and thrombocytosis suspected to be due to CML with myeloblasts totaling 6%. Examination of bone marrow aspiration showed a picture consistent with the chronic phase of CML where it appeared hypercellular with the discovery of a myeloid series stage (myeloblasts to neutrophil segments) and 3% of myeloblasts were found. PCR examination showed the presence of BCR-ABL transcription in the form of a b2a2 fusion, which encodes the protein p210 (major breakpoint).

During the 8 days of being treated and receiving analgesic therapy, complaints of pain in the groin decreased then the patient received TKI therapy, namely nilotinib at a dose of 200 mg every 12 times for 7 days but the pain returned on a severe scale so the therapy was changed to imatinib 200 mg per day. After 1 month of therapy with imatinib, the therapy regimen was again changed to nilotinib 200 mg every 12 hours because after a smear examination of the peripheral blood, the result was normochromic normocytic anemia with leukocytosis. After 1 month of receiving nilotinib therapy, another peripheral blood smear was examined with the results of normocytic normochromic

anemia with normal leukocyte counts. Complete blood examination was then carried out again with the results of hemoglobin 9.3 gr/dL, leukocytes 4.58 /uL, platelets 160,000 /uL, MCV 96.0 fL, MCH 33.0 pg. An x-ray pelvic examination was carried out with complaints of pain in the groin which the patient felt again. Pelvic x-ray examination showed an osteolytic lesion on the right femur which visualized suspected metastatic process. Examination was continued with a bone survey and obtained osteolytic lesions of the right femoral head and major throchanter susp metastatic bone disease with cor and pulmo that looked normal.

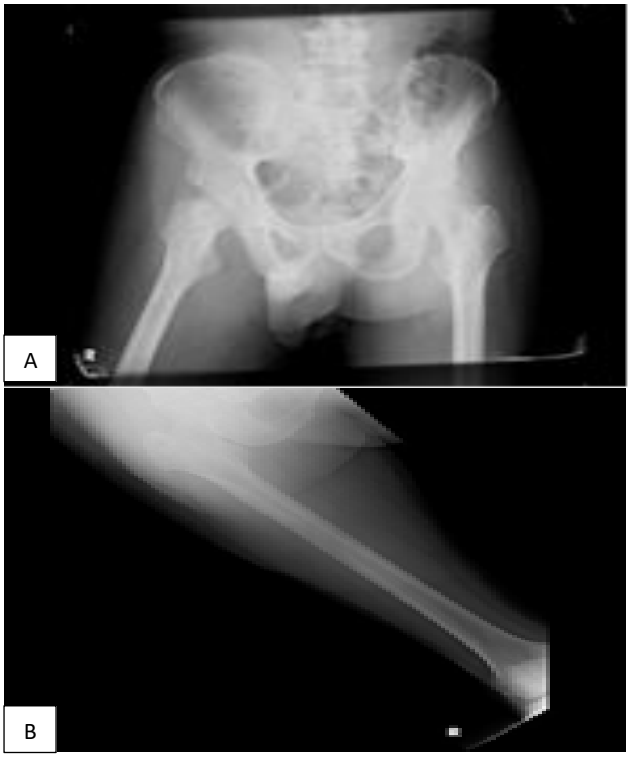

Figure 1 (A and B): Bone survey pelvic examination of the AP and the femur dextra AP showed osteolytic lesions of the right femoral head and major throchanter with susp metastatic bone disease.

After 7 months of nilotinib therapy, complaints of pain in the groin were still felt, so a pelvic xray and femur xray examination were carried out which showed an AVN of the left hip gr IV according to the ficat and arlet classification, where the picture matched the manifestations of leukemia in the head, neck to 1/3 proximal os of the dextra femur and the ischium to the left pubic inferior ramus and there is a picture of osteopenia in the bilateral femur. After 8 months of receiving nilotinib therapy, a complete blood count was performed again and it was found that the patient had thrombocytopenia where the platelets were 63,000 /uL so that the dose of nilotinib was reduced to 150 mg every 12 hours. Then 1 month later a re-evaluation was carried out and the thrombocytopenic condition still persisted with platelets 38,000 /uL so that nilotinib was stopped for 2 weeks. After the platelets slowly increased, the dose of nilotinib was started again until the final platelets reached 118,000/µL with a dose of 200 mg nilotinib every 12 hours.

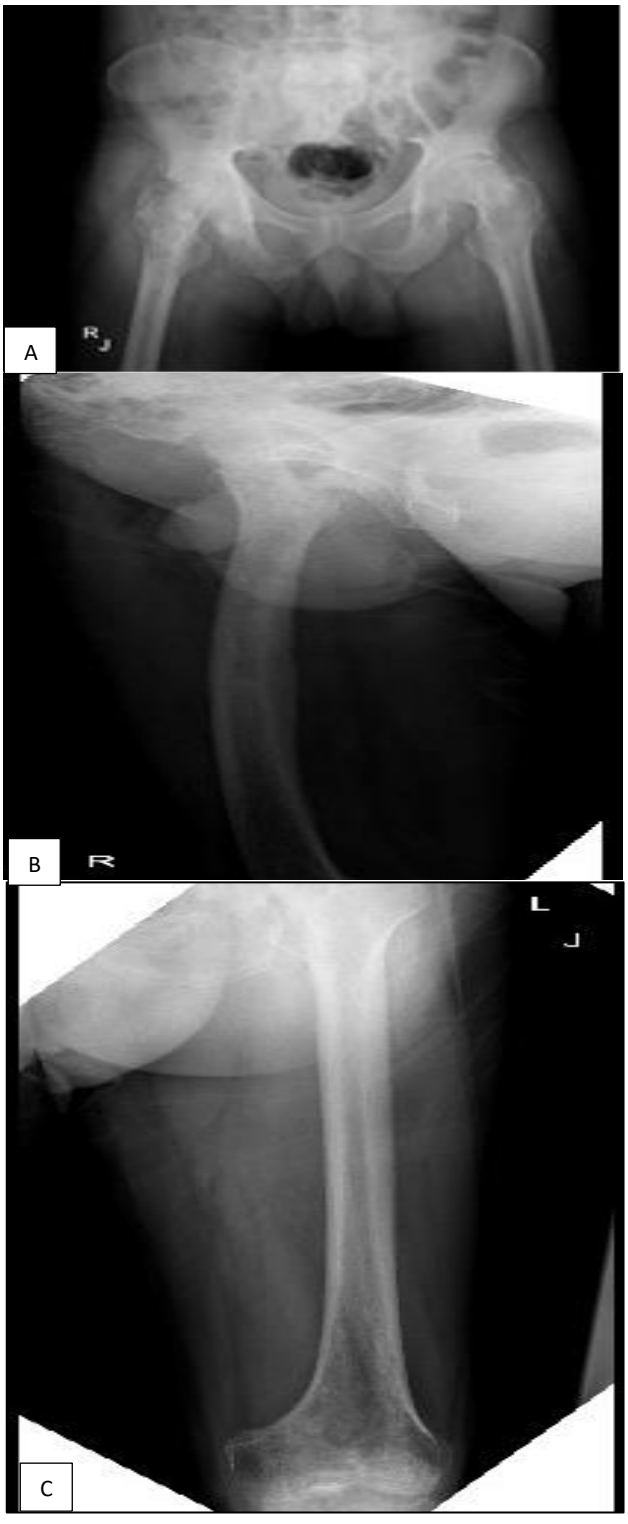

Figure 2 (A-C): On AP pelvic xray examination, the AP dextra femur and the AP left femur showed osteolytic lesions of the head, neck up to 1/3 proximal of the dextra femur and ischium bone to the left inferior pubic ramus. Subchondral cyst and subchondral sclerosis were seen in the left acetabulum and right femoral head.

Then the patient was consulted to Orthopedics and a pelvic xray and femur xray were examined. The results of the second radiological examination showed the same results so it was planned to undergo a total hip replacement surgery.

DISCUSSION

CML is characterized by a chronic phase lasting 3-5 years, followed by an accelerated phase and a blastic phase. In the chronic phase, manifestations such as anemia, splenomegaly, bleeding may occur, and constitutional symptoms such as fatigue, weakness, weight loss and fever. The presence of secondary symptoms such as leukostasis can be correlated clinically.[1,2]

Skeletal lesions are extremely rare in the chronic phase of CML accounting for approximately 3-5% of all cases. Various bone lesions in CML can be osteolysis, osteoporosis, osteosclerosis, periosteal reactions and fractures.[10] Skeletal lesions in the chronic phase of CML can become areas of ectopic myeloid metaplasia which is the first sign of the accelerated phase which later becomes the blastic phase. Bone pain is a major symptom that appears in patients with skeletal lesions or occurs before abnormalities are detected radiologically.[5] AVN in CML is more common at a younger age with an average age of 14.5±5.8 years. Juvenile skeleton increases the risk of AVN in CML with hyperleukocytes. Osteonecrosis is caused by hypervascularization of the juvenile femoral head and this explains why AVN is rarely found in adult CML cases.[11] A systematic review by Al-Mashdali et al which collected 18 scientific articles from 1984 to 2021 stated that there were 21 cases of AVN. in adult CML patients the median age was 39 years and the ratio between males and females was 1:1.[9] In this case the patient was a 51 years old male who had complaints of fever and pain in the groin.

Various traumatic and nontraumatic factors contribute to the etiology of AVN but are more commonly due to trauma. In adult patients, corticosteroid use and excessive alcohol intake are risk factors in more than 90% of cases. Nontrauma risk factors for AVN are the presence of systemic lupus erythematosus, antiphospholipid antibodies, sickle cell hemoglobinopathies, Gaucher's disease, congenital thrombophilia, or HIV infection.[4,8] The mechanism of AVN in CML is triggered by several conditions such as leukostasis, compression of blood vessels by leukemic foci or vascular obstruction by microthrombi associated with DIC.[9] AVN most commonly occurs at the anterolateral femoral head but can occur at the humeral head, femoral condyles, proximal tibia, vertebrae, and small bones of the hands and feet. Many patients have bilateral involvement of the pelvis, knees, and shoulders when diagnosed with AVN.[2] In cases there are osteolytic lesions of the head, neck up to 1/3 proximal os femur dextra and os ischium to the left inferior ramus pubis. Subchondral cyst and subchondral sclerosis were seen in the left acetabulum and right femoral head.

Leukostasis is a complication of CML characterized by partial or total occlusion of the microcirculation by leukemic cells and thrombus leading to respiratory, ophthalmic and neurological symptoms.[10] Additional but less common clinical findings include distended neck veins, gallop and myocardial ischemia, priapism, acute limb ischemia, infarction intestinal obstruction, renal vein thrombosis, bilateral deafness, and AVN.[2,6] The mechanism of AVN in CML is still not understood but there are several theories put forward including leukostasis, vascular compression by leukemic foci or vascular obstruction by microthrombi in DIC.[9] In a case report by Gupta et al who performed a core biopsy of the femoral head of a CML patient with AVN and found hypercellular leukemic foci, so it was thought that leukemic deposits could cause vascular compression which is the mechanism for the appearance of AVN. Thrombocytosis can induce micro-vessel thrombus which is a triggering factor for AVN.[5,10] The patient in this case early in the course of the disease experienced thrombocytosis and leukocytosis which triggered the condition of leukostasis and contributed to the mechanism for the emergence of AVN.

Some patients have symptoms of leukostasis with leukocytes above 100,000/mm. Leukemic myeloblasts have a larger mean cell volume (MCV) than lymphoblasts, so leukostasis is more common in AML or CML than in patients with ALL or CLL. Lekostasis can also occur due to interactions between the blast and endothelial cells. Complement-induced granulocyte aggregation is a leukostatic mechanism that has been extensively described in the literature. Several adhesion molecules (CD54, CD62E, CD62P, CD106) are upregulated in endothelial cells in AML patients with leukocytosis. Blast has the ability to secrete cytokines such as TNF-α and interleukin-1β which will trigger endothelium activation. Activation of the vascular endothelium by tumor necrosis factor-alpha (TNF-α) will increase myeloblast adhesion.[2,8]

The development of CML therapy has gone through two eras, namely the era of interferon alpha and tyrosine kinase inhibitors. So far there have been 5 cases of AVN in CML patients receiving interferon alpha therapy. The mechanism for the occurrence of AVNFH in patients with CML on interferon treatment could be due to the interaction between CML and interferon alpha therapy which triggers leukocytosis or thrombocytosis, causing microcirculation occlusion and leading to inhibition of angiogenesis, and the presence of weight-bearing loads on the femoral head makes it more vulnerable. The second era for the treatment of CML began with the use of tyrosine kinase inhibitors (TKI). Several cases of AVNFH have been reported in CML with first-generation TKI therapy with imatinib (Glivec®).[4,13] Nataraj et al reported a pediatric case with AVNFH related to Imatinib therapy.[14] A case report of dasatinib-related AVNFH was reported by Yassin et al.[4] Imatinib has an effect similar to interferon alpha, namely inhibiting angiogenesis, mainly through inhibition of the Platelet-derived growth factor receptor

(PDGFR) and c-Kit which reduces the expression of vascular endothelial growth factor (VEGF). Imatinib has a direct effect on the bone remodeling process. AVN has also been reported in patients receiving other TKI therapies such as desatinib and nilotinib and the mechanism is likely to be similar to that of Imatinib. Thus TKI, especially Imatinib, should be considered as a potential predisposing factor for AVN in CML patients.[9]

AVN can be treated pharmacologically/conservatively or surgically, but with the aim of therapy that is more palliative in nature, because currently there is no proven treatment that can totally stop the progression of the disease. Hip replacement surgery is the last resort for managing pain and achieving functional goals. AVNFH can complicate CML due to hyperviscosity and leukostasis. Awareness about complications will assist in early diagnosis and management.[10,11]

CONCLUSION

AVN in CML is a very rare condition but can cause high morbidity and long-term sequelae. AVN should be considered in patients with CML who present with joint pain. AVN in CML patients often attacks the femoral head. Early detection and appropriate treatment are needed to detect the presence of AVNFH in CML patients. AVN can be treated pharmacologically/conservatively or surgically, but the goal of therapy is more palliative.

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