Hypercalcemia and Multiple Pathological Fractures in Chronic Lymphocytic Leukaemia: A Case Report

Güçhan ALANOĞLU*, Simten DAĞDAŞ, Zeynep AKI**, Fırat YAĞMURLU***, Gülsüm ÖZET****

* Department of Haematology, Süleyman Demirel University School of Medicine, Isparta,
** Department of Haematology, Ankara Numune Hospital, Ankara,
*** Department of Orthopaedic Surgery, Ankara Numune Hospital, Ankara, TURKEY

ABSTRACT

Hypercalcemia is common in some lymphoproliferative disorders such as myeloma or T- cell leukaemia-lymphoma, but is rarely described in B-cell chronic lymphocytic leukaemia (CLL). A CLL patient who have been presented with multiple pathological fractures and widespread osteolytic lesions is reported. He was a 74 year old male with fractures of his bilateral humerus and radii and multiple osteolytic lesions of skull, fibula, femur and costals. On his admission to the hospital for the fractures he has been diagnosed as CLL. Hypercalcemia has also been documented. All the disorders that could be the reason of hypercalcemia have been ruled out. The open biopsy of bone marrow showed lymphocytic infiltration in which increased number of prolymphocytes are observed. Hypercalcemia arising in a patient with CLL may indicate a negative prognosis.

Key Words: Chronic lymphocytic leukaemia, Hypercalcemia, Pathological fractures.

ÖZET

Hiperkalsemi ve Çoğul Patolojik Kırıklar ile Başvuran Kronik Lenfositer Lösemi Olgusu

Hiperkalsemi, miyelom ya da T-hücreli lösemi-lenfoma gibi bazı lenfoproliferatif hastalıklarda sıkça görülmektedir. Ancak B-hücreli kronik lenfositer lösemi (KLL) de nadiren tarif edilmiştir. Yaygın osteolitik lezyonlar ve çoğul patolojik kırıklar ile başvuran bir KLL olgusu sunulmaktadır. Hasta 74 yaşında erkek olup bilateral humerus ve radius kırığı ve kafa, fibula, femur ve kostalarda çoğul osteolitik lezyonlar ile başvurdu. Daha sonra yapılan ileri incelemede KLL saptandı. Ayrıca hiperkalsemi de eşlik ediyordu. Hiperkalsemi etkeni olabilecek tüm nedenler araştırıldı ve dışlandı. Açık kemik iliği biyopsisi lenfosit infiltrasyonu olarak yorumlanırken prolenfositlerde artış gözlendiği rapor edildi. KLL'li bir hastada; klinik seyir sırasında hiperkalseminin ortaya çıkması negatif bir prognostik kriter olarak yorumlanabilir.

Anahtar Kelimeler: Kronik lenfositer lösemi, Hiperkalsemi, Patolojik kırık.

Turk J Haematol 2003;20(3): 167-170

Received: *21.01.2003* ***Accepted:*** *24.03.2003*

INTRODUCTION

Hypercalcemia is a well known complication of many malignancies. Among haematological malignancies it is most frequently seen in multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL), mainly of T-cell lineage. Pathogenetic mechanisms of osteolytic bone lesions are production and secretion of either a parathyroid-like hormone (PTHrP) or an osteoclast activating factor, $1,25(OH)_2D$ vitamin by the neoplastic cells and concurrent primary hyperparathyroidism[1]. In this report, we describe a patient who presented with multiple pathological fractures and diagnosed as CLL. Coexisting hypercalcemia is an important clinical significance for the negative prognosis of the disorder.

A CASE REPORT

A 74-year-old male admitted to the department of orthopedic surgery because of bilateral humerus shaft and proximal radius fractures. It was learned that the fractures developed after a minor trauma. He had been referred to the department of haematology when it was realized that he had a high white cell count. Physical examination showed generalized lymphadenopathy, no hepatosplenomegaly. Both upper extremities were stabilized by long arm splint. Hemoglobin was 11 g/dL, WBC 154 x 10^9/L with 90% mature lymphocytes and platelet count 283 x 10^9/L. ESR was 88 mm in 1 hr. Blood chemistry profile was as follows: Urea: 80 mg/L, corrected calcium 4.09 mmol/L, lactic dehydrogenase 631 IU/L, C-reactive protein 96 mg/L, parathormone concentration (intact PTH, solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay) was normal. The analysis of the urine was normal and Bence-Jones proteinuria was not detected. Polyclonal gammapaty was seen in serum protein electrophoresis. Peripheral blood findings revealed numerous small lymphocytic cells with condensed chromatin and several smudge cells. The percentage of prolymphocytes was < 10%. The membrane phenotype of these cells was positive for CD5, CD19, CD20 and expressed surface positivity for Kappa light chain. Bone marrow aspiration showed 90% small, mature lymphocytic infiltration. The open bone marrow biopsy performed from the fracture line showed lymphocytic infilration and no epitelial metastasis. The increase of prolymphocytes was interpretated as an aggressive form of CLL.

Radiological examination revealed, humeral shaft fractures with lytic lesions and seperated fracture line bilaterally (Figure 1). Both proximal radii showed destructive bone lesions. Also there were lytic lesions in both fibula diaphysis and skull. The bone scintigraphic scans (99Tc) displayed were as of high uptake in bilateral humerus diaphysis, proximal radii and low uptakes at bilateral femoral and tibial shafts and increased activity at several ribs (Figure 2). The search for other lymphoproliferative disorders and probable neoplasias which might cause osteolytic lesions was negative.

The case was evaluated as stage I (Rai staging system) CLL and had been rehydrated than received intravenous infusion of pamidronate (90 mg), cyclophoshamide (C) (500 mg for 5 day), vincristine (V) (2 mg on day 1), prednisone (P) (80 mg for 5 day) (CVP). Curetage, open reduction and fixation had been performed and remaining cavities were filled with bone cement. Three cycles of CVP were applied. During the follow-up the hypercalcemia has been reversed but the patient died because of systemic infection.

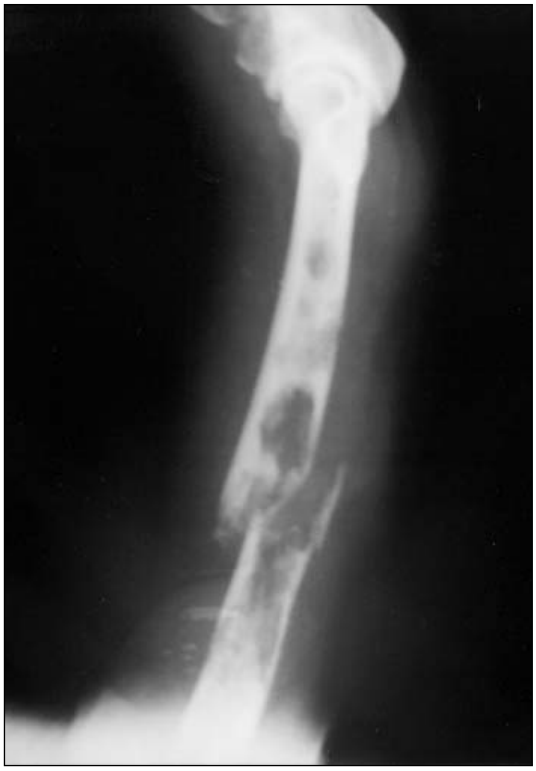

Figure 1. X-ray of humerus showing multiple lytic lesions and fracture line.

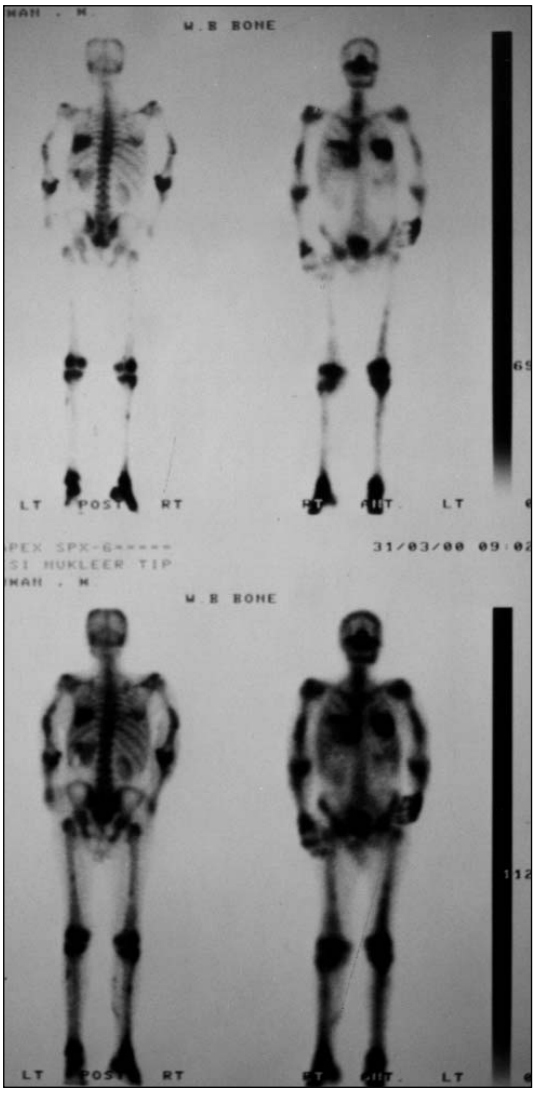

Figure 2. The bone scintigraphic scan showing the high uptake areas.

DISCUSSION

Malignancy associated hypercalcemia includes four major pathogenetic mechanisms: Firstly humoral mediated hypercalcemia is due to the production of parathyroid hormone related peptide (PTHrP) by the tumour cells. Secondly: Calcitriol mediated hypercalcemia with dysregulated production of calcitriol by the malignant cells. Thirdly localized bone resorption by activated osteoclasts in which, besides tumour metastasis, a variety of cytokines (IL-1ß, TNF-ß,IL-6) have also been shown. Finally; in some cases hypercalcemia can be due to coexistent primer hyperparathyroidism[1-4]. Hypercalcemia constitutes a well known complication of neoplastic disorders. Among haematologic malignancies, it is most frequently seen in multiple myeloma and non-Hodgkin's lymphoma (NHL), mainly of T-cell lineage[1-4]. Yet the combination of hypercalcemia with CLL is not well characterized. As far as CLL is concerned hypercalcemia has seldom been reported. In 1996 Vaturi evaluated 1200 B-CLL patients and 7 CLL patients with hypercalcemia were found[1]. It is of note that in the few patients with early CLL in whom hypercalcemia has been found, the latter has usually been associated with primary hyperparathyroidism[3]. Among patients without elevated levels of parathormon, hypercalcemia seems to herald a terminal stage of the disease[1,2].

The pathogenetic mechanism of hypercalcemia in CLL patients is not well established. Localized bone resorption by activated osteoclasts has been suggested as the main cause. Moreover although it has been demostrated that several cytokines such as TNF, IL-1, IL-6 which are potent stimulators of osteoclastic bone resorption in vitro, can be secreted by activated lymphocytes. Their role in CLL hypercalcemia is not clear[3,5]. Finally, the production of PTHrP has also been involved as a possible cause of hypercalcemia in CLL[2,3]. PTHrP production is generally associated with more advanced disease of high grade pathology[6,7]. Hypercalcemia is seen in 5% of Richter's syndrome which is a advanced stage of CLL[1,3].

Our patient had been admitted with pathological multiple fractures of humerus and radii. By the further evaluation CLL had been established. The coexistence of multiple fractures during the course of CLL is an unexpected manifestation[8]. As hypercalcemia was found; the pathologies that could result with hypercalcemia had been searched out. No other malignancy, nor MM had been detected. We could not perform parathyroid scanning, PTHrP and cytokine levels to evaluate the etiology of hypercalcemia. Hypercalcemia was diagnosed after a mean period of 4.14 years after following the diagnosis of CLL. Most of the patients were related to a high tumour burden[1]. We can not make a comment about the onset of our patients disorder. After three cycles of chemotherapy we had a decrease in hypercalcemia. Thus the patient died because of septicemia. The clinical course and the aggresive pattern of

the lymph node biopsy revealed that this case had an advanced stage by hypercalcemia.

During the follow up of a low grade lymphoproliferative disease if hypercalcemia appears it may indicate a poor prognostic criteria.

REFERENCES

1. Vaturi M, Prokocimer M, Sidi Y. Hypercalcemia in chronic lymphatic leukemia patients. Am J Hematol 1996;53:245-7.
2. Fain O, Selmi A, Dosquet C, Meseure D, Lejeune F, Garel JM, Thomas M. Hypercalcemia in B-cell chronic lymphocytic leukemia. Br J Haematol 1994;87: 856-8.
3. Briones J, Cervantes F, Montserrat E, Rozman C. Hypercalcemia in a patient with chronic lymphocytic leukemia evolving into Richter's syndrome. Leuk Lymphoma 1996;21:521-3.
4. Beaudreuill J, Lortholary O, Martin A, Feuillard J, Guillevin L, Lortholary P, Raphael M, Casassus P. Hypercalcemia may indicate Richter's syndrome: Report of four cases and review. Cancer 1997;79: 1211-5.
5. Van de Casteele M, Verhoef GEG, Demuynck H, Zacheé P, Boogaerts MA. Hypercalcemia, monoclonal protein, and osteolytic bone lesions in chronic lymphocytic leukemia. Ann Hematol 1994;69:79-80.
6. Kremer R, Shustik C, Tabak T, Papavasiliou V, Goltzman D. Parathyroid-hormone-related peptide in hematologic malignancies. Am J Med 1996;100: 406-11.
7. Davies SV, Vora J, Wardrop CAJ. Parathyroid hormone related protein (PTHrP) in hypercalcemia of lymphoproliferative disease. J Clin Pathol 1993; 46:188.
8. Çağırgan S, Şencan M, Dönmez A, Özdemir E, Tombuloğlu M, Büyükkeçeci F. A case report: Chronic lymphocytic leukemia with widespread osteolytic lesions. Turk J Haematol 1997;14:113-5.

Address for Correspondence:

Güçhan ALANOĞLU, MD

İstasyon Caddesi 32/9
32300, Isparta, TURKEY

e-mail: *guchanalanoglu@yahoo.com*