

Hypercalcemia with multiple osteolytic lesions and increased circulating tumor necrosis factor in an adult patient with B-cell acute lymphoblastic leukemia

Marijana Virijević¹, Ana Vidović^{1,2}, Nataša Čolović^{1,2}, Irena Djunić^{1,2}, Mirjana Mitrović^{1,2}, Nada Suvajdžić-Vuković^{1,2}, Dragica Tomin^{1,2}

¹Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia;

²University of Belgrade, School of Medicine, Belgrade, Serbia

SUMMARY:

Introduction Acute lymphoblastic leukemia (ALL) is very rarely presented with diffuse osteolytic lesions and hypercalcemia.

Case Outline We report a 28-year-old male with the B-cell ALL who presented with extensive osteolytic lesions, bone pain, hepatosplenomegaly, and pancytopenia without circulating blasts in peripheral blood. An increased serum level of tumor necrosis factor (TNF- α) was registered while the levels of IL-1 α and IL-1 β were normal. The patient failed to achieve remission on two induction regimens but achieved one after the successful allogeneic stem cell transplantation, which lasted for six months, after which he developed a relapse and died.

Conclusion The presented case may serve as a clinical demonstration of possible involvement of TNF- α as a pathogenic factor in the evolution of osteolytic lesions that are occasionally observed in patients with ALL. This might have relevance in the management of such patients as chemotherapy alone may not represent the beneficial option in this clinical context.

Keywords: acute lymphoblastic leukemia; hypercalcemia; osteolytic lesions, TNF- α

INTRODUCTION

Bone osteolytic lesions and hypercalcemia are rare events in most hematologic malignancies, except in patients with multiple myeloma and in adult T-cell leukemia/lymphoma (ATLL) patients associated with human T-cell leukemia/lymphoma virus-1 [1, 2]. Many bone regulatory factors secreted by cancer cells that activate osteoclasts may induce hypercalcemia and osteolytic lesions [3].

Only individual cases of osteolytic lesions in adult patients with acute lymphoblastic leukemia (ALL) have been reported. Predictive prognostic significance of bone lesions is still unclear. We report an adult male patient with B-ALL who presented with multiple osteolytic lesions in all bones together with hypercalcemia.

CASE REPORT

A 28-year-old man was admitted to the Clinic of Hematology with complaints of exhaustion, loss of 15 kg in weight, fever, and bone pains of two-month duration. On examination, hepatosplenomegaly without lymphadenopathy and hemorrhagic syndrome were found. Complete blood count was as follows: hemoglobin – 107 g/L, white blood cell count – $3.0 \times 10^9/l$, without blasts and platelet count – $24 \times 10^9/l$ (Table

1). He had an increased calcium concentration (2.6 mmol/L), with normal level of phosphate and magnesium. Serum alkaline phosphatase (228 U/l), lactate dehydrogenase (1,527 U/l) and uric acid (644 μ mol/l) levels were all elevated. Serum and urine electrophoresis did not reveal the “M” component. Bone marrow aspirate showed 70% POX negative blasts. Flow cytometry confirmed B-common ALL: HLA-DR, CD34, CD19, cCD79a, CD24, CD22, CD10, CD33, with aberrant expression of CD33. Cytogenetic analysis revealed a normal karyotype. Reverse transcriptase-polymerase chain reaction analysis did not detect bcr/abl fusion gene. Flow cytometry of cerebrospinal fluid (CSF) was negative for malignant cells. Laboratory findings of hypercalcemia-associated parameters also showed a high level of parathyroid hormone (92 ng/l) and a low level of 1,25-dihydroxyvitamin D (38 nmol/l). Tumor necrosis factor (TNF- α), IL-1 α and IL-1 β were determined by enzyme-linked immune sorbent assay. The serum concentration of TNF- α was increased, while levels of IL-1 α and IL-1 β were within normal limits (Table 2). A skeletal radiography showed extensive osteolytic lesions involving the skull, pelvis, ribs and long bones (Figures 1). The spine CT scan confirmed multiple osteolytic lesions in all vertebrae, as well as vertebral compression fractures of Th10 and Th11 (Figure 2).

Correspondence to:

Marijana VIRIJEVIĆ
Clinic for Hematology
Clinical Center of Serbia
Koste Todorovića 2
11000 Belgrade
Serbia
marijana.virijevic@yahoo.com

Table 1. Laboratory data at diagnosis

Laboratory parameters	At diagnosis	Normal range
Blood urea nitrogen	4.3	(4.1–5.9 mmol/l)
Creatinine	80	(58–110 μ mol/l)
Calcium	2.19 (2.6) (H)	(2.10–2.55 mmol/l)
Magnesium	0.81	(0.7–1.15 mmol/l)
Phosphorus	1.43	(0.80–1.55 mmol/l)
Albumin	21 (L)	(35–50 g/l)
Alkaline phosphatase	228 (H)	(38–126 U/l)
Lactate dehydrogenase	1527 (H)	(313–618 U/l)
Uric acid	644 (H)	(208–506 μ mol/l)
Hemoglobin	107 (L)	(130–180 g/l)
White blood cell count	3 (L)	(4–10 \times 10 ⁹ /l)
Platelet count	24 (L)	(150–450 \times 10 ⁹ /l)

H – high; L – low

Table 2. Hypercalcemia-associated parameters at diagnosis

Parameters	At diagnosis	Normal range
PTH	92	(15–62 ng/l)
1,25-OH Vitamin D	38 (L)	(>75 nmol/l)
Calcitonin	<2	(0–8.4 ng/l)
TNF- α	74 (H)	(0.0–8.1 ng/l)
IL-1 α	1.5	(0.0–3.9 pg/ml)
IL-1 β	<5.0	(0.0–5.0 pg/ml)

PTH – parathyroid hormone; TNF- α – tumor necrosis factor alpha; IL – interleukin; H – high; L – low

Initially, the patient was treated with furosemide, corticosteroids, and analgesics. Induction chemotherapy included cyclophosphamide, doxorubicin, vincristine, and dexamethasone according to the hyper-CVAD regimen, but did not achieve complete remission after completion of the first cycle of this regimen or after receiving FLAG-IDA (fludarabine, cytarabine, G-CSF, idarubicin) salvage therapy, so a contralateral myelogram showed 20% of blasts. As he had a completely identical human leukocyte antigen sibling donor, allogeneic stem cell transplantation was performed, which led to complete remission, radiographic reductions of osteolytic lesions, and to normal TNF- α concentration. Six months later, the patient developed pain in bones and increased blood calcium level. Bone marrow examination confirmed the relapse of the disease, resulting with fatal outcome.

DISCUSSION

The reported case shows some unusual initial features of adult ALL. The atypical presentation included multiple osteolytic lesions, hepatosplenomegaly, pancytopenia without blasts in peripheral blood and the absence of lymphadenopathy. Before hematological diagnosis was established, certain non-hematological malignancies, non-Hodgkin lymphoma, and multiple myeloma, were taken into consideration.

The condition is rare. So far, only a few cases with similar characteristics in adult patients with ALL have been described, all with multiple osteolytic lesions and hypercalcemia [4–9]. An increased level of TNF- α , together with elevated levels of IL-6 and IL-2 were reported in one case, and the involvement of parathyroid hormone related protein (PTHrP) in another [8, 10]. After chemotherapy, calcium concentration in our patient dropped to the normal level but hypercalcemia reappeared at the relapse of the disease. The same features had been described earlier in two young patients with ALL [4, 11].

Hypercalcemia is a common complication in patients with some malignant disorders, but it is very rare in patients with ALL. Thus, the incidence of hypercalcemia varied 50–90% in ATLL, 27–35% in lung cancer, 25–30% in breast cancer, 7–30% in multiple myeloma, but less than 10% in malignant lymphoma, and even less than 1% in leukemia patients [1].

The pathogenic mechanism of osteolytic bone lesions and hypercalcemia in ALL is still unknown. Bone lesions could be attributed to local osteolytic hypercalcemia in which factors secreted either by primary or metastatic tumor cells in the bone microenvironment might stimulate osteoclastic bone resorption locally, as was already recorded in multiple myeloma and in ATLL [2]. An increased osteoclastic bone resorption induced by humoral mediators produced by tumor cells or by bone marrow stromal cells could be the cause as well [2]. PTHrP is known as an important humoral factor in most cases of cancer-induced hypercalcemia [12]. Three reported cases of ALL with hypercalcemia exhibited an increased serum PTHrP concentration associated with hypercalcemia [5, 6, 10]. Proinflammatory cytokines, such as TNF- α , IL-1,

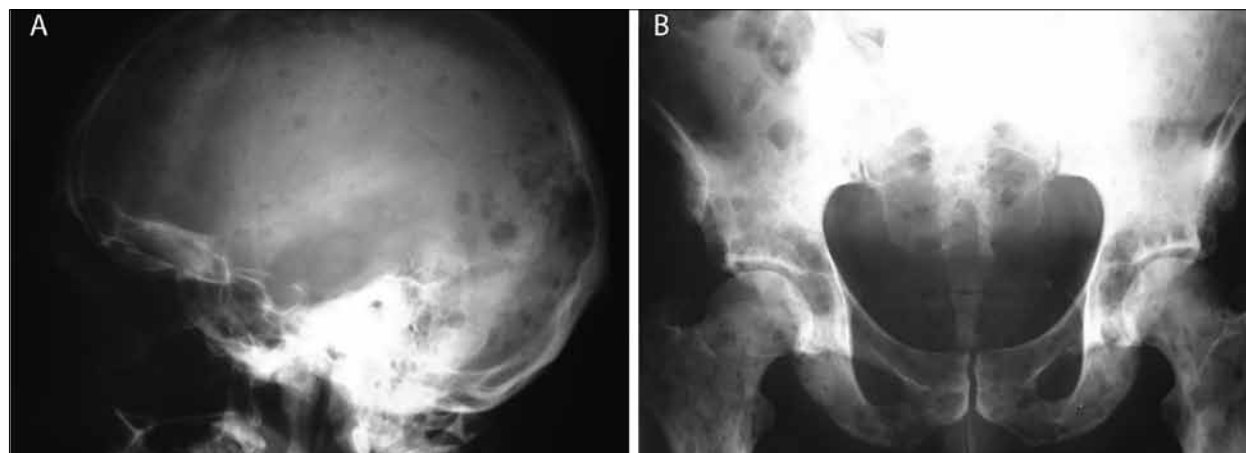
**Figure 1.** Multiple osteolytic lesions in the skull and pelvis (A and B)



Figure 2. CT scan of spine showing numerous osteolytic lesions in all vertebrae, and vertebral compression fractures Th10 and Th11

and IL-6 have been shown to play an important role in the pathogenesis of hypercalcemia in malignant disorders [3, 13].

These mediators promote bone resorption by activation of osteoclasts via the interaction of receptor activator of nuclear factor- κ B (RANK) on osteoclasts with RANK ligand on osteoblasts or stromal cells [13]. Increased serum level of TNF- α was described in patients with ALL as pro-inflammatory cytokines that are associated with multiple osteolysis and hypercalcemia [7, 8, 10].

The prognostic significance of multiple osteolytic lesions and hypercalcemia in patients with ALL is not clear. Several retrospective studies have been performed in children to evaluate the impact of bone lesions on the prognosis in pediatric leukemia patients, but predicting value stayed controversial as some investigations were in favor of worse prognosis [14, 15], while others showed either improved prognosis or no impact [16, 17].

B-ALL with multiple osteolytic lesions manifested as an aggressive form of the disease in the presented patient. The increased serum level of TNF- α in the patient may have contributed to the osteolytic bone lesions and hypercalcemia and could have been associated with the poor prognosis and outcome.

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Хиперкалцемија са мултиплим остеолитичним лезијама и повећаним циркулишућим фактором некрозе тумора код одраслог болесника са В-ћелијском акутном лимфобластном леукемијом

Маријана Виријевић¹, Ана Видовић^{1,2}, Наташа Чоловић^{1,2}, Ирена Ђунић^{1,2}, Мирјана Митровић^{1,2}, Нада Сувајцић-Вуковић^{1,2}, Драгица Томин^{1,2}

¹Клиника за хематологију, Клинички центар Србије, Београд, Србија;

²Универзитет у Београду, Медицински факултет, Београд, Србија

КРАТАК САДРЖАЈ

Увод Акутна лимфобластна леукемија се ретко презентује са дифузним остеолитичним лезијама и хиперкалцемијом.

Приказ болесника Аутори приказују 28 година старог болесника са В-ћелијском акутном лимфобластном леукемијом, код кога су у време постављања дијагнозе биле присутне дифузне остеолитичке лезије, болови у костима, хепатоспленомегалија и панцитопенија без присуства бласта у периферној крви. У серуму је нађен повећан ниво фактора некрозе тумора алфа (*TNF-α*), док је ниво *IL-1α* и *IL-1β* био у границама референтних вредности. Пацијент није повољно реаговао на две индукционе хемотерапије, али је након

успешно спроведене алогене трансплантације матичних ћелија хематопоезе постигао ремисију која је трајала шест месеци, након чега је уследио релапс и брз летални исход.

Закључак Приказ говори у прилог могућем учешћу *TNF-α* као патогеног фактора у настанку остеолитичних лезија које се повремено запајају код болесника са акутном лимфобластном леукемијом, што може бити од значаја и у терапијском приступу када се у овом клиничком контексту хемотерапија покаже неуспешном.

Кључне речи: акутна лимфобластна леукемија; хиперкалцемија; остеолитичке промене; *TNF-α*

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