Severe Hypercalcemia Indicating Relapse of Acute Myelocytic Leukemia after Bone Marrow Transplantation

J.	Jesús	Montoliu
J.	Josep	Maciá
P.	Pere	Salamero
R.	Rafael	Parra
M.	Miquel	Gallart

Nephrology and Hematology Services, Hospital Arnau de Vilanova, Lleida; Faculty of Medicine, Estudi General de Lleida, 6th Division of the University of Barcelona, Lleida, Spain

Dr. Jesús Montoliu, Nephrology Service, Hospital Arnau de Vilanova, Rovira Roure 80, E-25006 Lleida (Spain)

Sir,

Hematologic malignancies, particularly multiple myeloma, are common causes of hypercalcemia. Other types of hematologic cancer where hypercalcemia can be found include Hodgkin's and non-Hodgkin's lymphoma and adult T-cell leukemia caused by human T-cell lymphotropic virus type I [1-3]. The present report describes a patient with acute myelocytic leukemia that underwent bone marrow transplantation and in whom relapse of leukemia presented clinically as severe hypercalcemia.

A 32-year-old man presented in May 1988 with fever, gum hypertrophy and splenomegaly. He had a total white blood cell (WBC) count of $222 \times 10^9/l$, with 90% blasts, some of them with Auer rods. Hemoglobin was 128 g/l and the platelets were $48 \times 10^9/l$. A bone marrow examination showed complete invasion by blast cells, and after histo-chemistry and cell markers he was diagnosed as having acute myelocytic leukemia, class M1 by the French-American-British (FAB) classification. At that point, his serum calcium was normal (2.19 mmol/l), as well as his serum creatinine and urinary sediment. He was treated with daunoblastin, VP 16 and cytosine arabinoside with good response and apparent complete remission in the bone marrow and peripheral blood. He underwent later 2 consolidation treatments. One month after the 2nd consolidation treatment (October 1988) he was in complete remission.

In early April 1989, he was found to be in relapse. A bone marrow biopsy disclosed 50% infiltration by blast cells. He was treated with cytosine arabinoside and mitoxantrone and achieved complete remission 23 days after chemotherapy. During his first relapse, serum calcium was still normal (2.2 mmol/l).

In June 1989, he underwent successful bone marrow transplantation from an HLA identical brother. Throughout the period of bone marrow transplantation, he maintained normal serum calcium levels. In early December 1989, he was asymptomatic and in complete remission. His serum calcium was 2.27 mmol/l and medications consisted of low-dose ciclosporin and prednisone, 30 mg on alternate days for grade I graft versus host disease. He was readmitted to the Hospital on December 24, 1989, with a 3-day history of marked weakness, vomiting

and myalgia in the legs. Physical examination was essentially normal. Both legs were weak, without any sign of neurological impairment. Laboratory tests gave the following results: hematocrit 0.42, hemoglobin 141 g/l, total WBC count $11.9 \times 10^9/l$ (differential: bands 2%, segmented 68%, lymphocytes 23%, monocytes 2% and 5% blasts on peripheral blood), platelets $169 \times 10^9/l$, blood glucose 5.8 mmol/l, serum calcium 4.04 mmol/l, serum phosphate 1.22 mmol/l, serum uric acid 0.98 mmol/l, total serum protein 62 g/l, serum albumin 40 g/l, serum creatinine 144 $\mu\text{mol/l}$, total serum bilirubin 14.5 $\mu\text{mol/l}$, serum alkaline phosphatase 108 U/l, serum aspartate aminotransferase 78 U/l, serum alanine aminotransferase 203 U/l, serum LDH 611 U/l,

©1992 S.Karger AG, Basel 0028-2766/92/
062.000357\$2.75/O

serum creatine kinase 3 U/l, γ -glutamyltrans-ferase 96 U/l, serum sodium 136 mmol/l, serum potassium 2.8 mmol/l, serum chloride 99 mmol/l, arterial pH 7.51, PCO₂ 45 mm Hg, PO₂ 121 mm Hg and serum CO₂ content 36 mmol/l. The urine contained no protein or red cells, and there were 2-3 WBC per high-power field. Urine creatinine was 5.215 $\mu\text{mol/l}$, urine sodium 30.5 mmol/l, urine potassium 24 mmol/l and urine chloride 16 mmol/l. Twenty-four-hour urinary calcium excretion was 12.4 mmol/l (measured 1 day after institution of hydration and furosemide). Serum intact PTH was $< 8.5 \text{ pg/ml}$ (normal range 10-65), serum 1,25-dihydroxyvitamin D₃ was 8.1 pg/ml (normal range 14-41), and serum 25-hydroxyvitamin D₃ was 4 ng/ml (normal range 8-80). Chest X-ray was normal and the EKG showed only shortening of the Q-T interval.

A bone marrow biopsy demonstrated 50% infiltration by nonlymphoblastic blast cells. After histochemistry and cell markers, the leukemia relapse was classified again as acute myelocytic (M1 by the FAB classification), identical to the original one. A bone survey including the skull, spine, ribs, pelvic and long bones, hands and feet, showed no lytic lesions. The patient refused a bone scan.

The patient was initially treated with hydration, intravenous furosemide, intravenous potassium chloride, intravenous methylpred-nisolone and allopurinol. Four days later, serum calcium had been decreasing progressively to 2.89 mmol/l, serum creatinine was 88.4 $\mu\text{mol/l}$, and serum potassium was 3.4 mmol/l. The relapse of leukemia was treated initially with a combination of cytosine arabi-noside and thioguanine. After chemotherapy, serum calcium normalized and hypercalcemia did not recur. However, no bone marrow remission was achieved and the patient died of multiple complications. No autopsy was performed.

In this patient, the relapse of myelocytic leukemia became clinically manifest as severe hypercalcemia. Because of their clear temporal relationship and since other causes of hypercalcemia were reasonably ruled out, it can be concluded that the elevation in serum calcium was due to the relapse of leukemia. To the best of our knowledge, this has not been reported to occur previously. Neither ciclosporin nor graft versus host disease are known to cause hypercalcemia.

Although the clinical workup of our patient lacked a bone scan, no bone lesions were found in the bone survey, suggesting that hypercalcemia had a humoral mechanism. Hypercalcemia in hematologic malignancies

can be due to either local or humoral factors. Local factors are exemplified by the secretion of bone-resorbing cytokines by myeloma or lymphoma cells when in contact with bone. These cytokines include interleukin-1, tumor necrosis factor- α and tumor necrosis factor- β [3,4].

When malignant cells are remote from bone and secrete substances that stimulate osteoclastic bone resorption they give rise to humoral hypercalcemia. Two main mechanisms of humoral hypercalcemia in lymphoma have been described. On one hand, there are reports of increased 1,25-dihydroxy-vitamin D₃ levels, presumably as a result of secretion by the lymphoma cells [2,4]. Since 25-hydroxyvitamin D₃ and 1,25-dihydroxy-vitamin D₃ levels in our patient were normal, this mechanism can be ruled out. On the other hand, recent evidence suggests that most humoral hypercalcemia of cancer is mediated by a novel peptide that resembles parathyroid hormone (PTH) in some aspects but differs in others. This protein increases osteoclastic bone resorption and reduces urinary calcium excretion due to a rise in renal tubular calcium reabsorption coupled with an increase in nephrogenous cyclic AMP excretion [3,6,7]. These actions resemble those of PTH. However, this protein reacts poorly with PTH antiserum because it is structurally different from most part of the PTH molecule. The PTH-related protein shares similarity only with the amino-terminal portion of the PTH molecule, where the biological activity of PTH rests, because this is the part responsible for receptor binding. With this in mind, it can be understood why hypercalcemia of cancer seems to be, in some aspects, PTH mediated, while immunoreactive PTH levels are low or undetectable [3,6]. In our patient, the coincidence of severe hypercalcemia with the absence of lytic bone lesions, the decreased levels of immunoreactive serum PTH and the also decreased 25-hydroxy- and 1,25-dihydroxyvitamin D₃ serum levels are consistent with humoral, PTH-related protein-mediated hypercalcemia [3]. A similar pattern has been recently reported in hypercalcemia associated with adult T-cell leukemia caused by human T-cell lymphotropic virus [8]. With this exception, hypercalcemia is rare in other types of leukemia. It is uncertain why our patient had a normal serum calcium value when he first presented with the full-blown leukemic syndrome and became hypercalcemic only when leukemia relapsed in his bone marrow transplant, since apparently the original leukemia cells and those from the relapse belonged to a similar lineage and had an identical immunophenotype. It is clear, however, that the cells were nonlymphoblastic and totally devoid of T-cell antigens. Although its mechanism is not totally defined, clinicians should suspect relapse of leukemia when a bone marrow recipient develops hypercalcemia. In addition, acute myelocytic leukemia should be considered in the differential diagnosis of malignancy-associated hypercalcemia.

Acknowledgement

The authors thank Joan Gaya, PhD for the PTH and vitamin D determinations.

References

- Mundy R, Ibbotson KJ, D'Souza S, Simpson E, Jacobs JW, Martin TJ: The hypercalcemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med* 1984;310:1718-1727.
- Zaloga GP, Eil C, Medbery CA: Humoral hypercalcemia in Hodgkin's disease: Association with elevated 1,25-dihydroxycholecalciferol levels and subperiosteal bone resorption. *Arch Intern Med* 1985;145:155-157.
- Broadus AE, Mangin M, Ikeda K, et al: Humoral hypercalcemia of cancer: Identification of a novel parathyroid-hormone-like peptide. *N Engl J Med* 1988;319:556-563.
- Garret IR, Durie BGM, Nedwin GE, et al: Production of lymphotoxin, a bone-resorbing cytokine by cultured human myeloma cells. *N Engl J Med* 1987;317:526-532.

Breslau NA, McGuire JL, Zerwekh JE, Frenkel EP, Pak CYC: Hypercalcemia associated with increased serum calcitriol levels in three patients with lymphoma. *Ann Intern Med* 1984;100:1-7.

Ralston SH: The pathogenesis of humoral hypercalcemia of malignancy. *Lancet* 1987;ii: 1443-1446.

Budayr AA, Nissenson RA, Klein RF, et al: Increased serum levels of a parathyroid-hormone-like protein in malignancy-associated hypercalcemia. *Ann Intern Med* 1989;iii: 807-812.

Fukumoto S, Matsumoto T, Ikeda K, et al: Clinical evaluation of calcium metabolism in adult T-cell leukemia/lymphoma. *Arch Intern Med* 1988;148:921-925.

358

Montoliu/Maciá/Salamero/Parra/Gallart

Hypercalcemia in Acute Myelocytic Leukemia