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 × 10^7/l, with 90% blasts, some of them with Auer rods. Hemoglobin was 128 g/l and the platelets were 48 × 10^7/l. A bone marrow examination showed complete invasion by blast cells, and after histochemistry 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 mitroxantrone 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 11.9x10^7/L, (differential: bands 2%, segmented 68%, lymphocytes 23%, monocytes 2% and 5% blasts on peripheral blood), platelets 169 × 10^7/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 creatinine 144 µmol/L, total serum bilirubin 14.5 µmol/L, serum alkaline phosphatase 108 U/L, serum aspartate aminotransferase 78 U/L, serum alanine aminotransferase 203 U/L, serum LDH 61 U/L, serum creatine kinase 3 U/L, γ-glutamyltranspeptidase 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 µmol/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 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 histochcmistry 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 methylprednisolone and allopurinol. Four days later, serum calcium had been decreasing progressively to 2.89 mmol/L, serum creatinine was 88.4 µmol/L, and serum potassium was 3.4 mmol/L. The relapse of leukemia was treated initially with a combination of cytosine arabinoside 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
$\text{I,25-dihydroxy-vitamin D}_3$ levels, presumably as a result of secretion by the lymphoma cells
[2,4]. Since 25-hydroxyvitamin D$_3$ and $\text{I,25-dihydroxy-vitamin D}_3$ 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
antisera 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 $\text{I,25-dihydroxyvitamin D}_3$ 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
1727.
with elevated $\text{I,25-dihydroxycholecalciferol}$ levels and subperiosteal bone resorption. Arch
Garrett IR, Durie BGM, Nedwin GE, et al: Production of lymphotoxin, a bone-resorbing cyto-

