Complex Biochemical Syndrome of Hypocalcemia and Hypoparathyroidism during Cytotoxic Treatment of an Infant with Leukemia

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Patients with cancer are especially vulnerable to the development of hyper- and hypocalcemia. These disorders may be the basic clinical manifestation of cancer or may result from vigorous cancer treatment. During cytotoxic treatment of a child with leukemia we describe the longitudinal course of ionized calcium in a complex syndrome of hypocalcemia and hypoparathyroidism. The results suggest that the development of severe hypocalcemia can be explained on the basis of hypoparathyroidism in relation to hyperphosphatemia, hypomagnesemia, and acute renal failure. The low ionized calcium was unsuccessfully treated with several doses of calcium levulinate but successfully treated with 1α-hydroxycholecalciferol.

Additonal Keyphrases: electrolytes • cancer • calcium metabolism

Advances in cytotoxic treatment in recent years have led to initial bone-marrow remission in more than 80% of the children with acute lymphoblastic leukemia.

However, because complications of infection, bleeding, and electrolyte disorders attributable to leukemia and to antileukemic therapy have become potentially lethal problems, it is important to anticipate and evaluate the different metabolic disorders such patients may encounter.

Hypokalemia and hyponatremia are well-known complications of cytotoxic therapy in leukemia and, though infrequent, hypocalcemia has also been reported (2, 2). A complex syndrome of hypocalcemia (serum total calcium), hyperphosphatemia, hypomagnesemia, and hypoparathyroidism was indicated recently in nine adults who were receiving cytotoxic treatment for leukemia (3).

Here we have systematically evaluated the biochemical basis for this syndrome in a case of acute lymphoblastic leukemia in a five-year-old boy after initial cytotoxic therapy. We examined the syndrome and monitored the successful treatment longitudinally by measuring ionized calcium and related analytes.

Case Report

A five-year-old boy was admitted to the pediatric department of Odense Hospital with a one-month history of respiratory disease, increasing weakness, intermittent fever, and distended abdomen. The pulse rate was 80 per minute and the temperature 37.3 °C.

Physical examination showed minor bleeding in the mouth and distinct cervical and inguinal lymphadenopathy. Respiration was decreased distal on the left, with mediastinum ectasia superior. His abdomen was distended, and the liver and especially the spleen were enlarged. Results of neurological examination were within normal limits. The initial concentration of leukocytes was 184 × 10⁹/L (Figure 1A), with 74% lymphoblasts.

The thrombocyte count was 134 × 10⁹/L, and the hemoglobin concentration was 7.6 mmol/L. A bone-marrow aspirate contained 84% lymphoblasts. The bone-marrow blasts were acid-phosphatase positive and peroxidase negative, indicating an acute lymphoblastic leukemia.

![Fig. 1. Sequential changes in biochemical quantities related to the renal function and calcium metabolism during complicated severe hypocalcemia in present case of acute leukemia.](image)

(A) leukocytes; (B) urea; (C) creatinine; (D) phosphate; (E) total calcium; (F) ionized calcium; (G) total magnesium; (H) parathyroid. Shaded areas represent reference intervals for these tests in our institution.

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The high leukocyte count and the mediastinal involvement placed this patient in a high-risk category of acute lymphoblastic leukemia. Initial laboratory values for serum were as follows: total calcium 2.44 mmol/L, phosphate 1.86 mmol/L, urate 0.64 mmol/L, and creatinine 136 µmol/L (Figure 1E, D, B, C).

Conventional therapy was started on the day of admission, with prednisolone, allopurinol, and sodium bicarbonate to lower the initial high urate concentration and to relieve the relatively poor renal function.

In our hospital the routine protocol for the antileukemic induction therapy consists of 21 daily doses of asparaginase (EC 3.5.1.1) administered intravenously (5000 U/m² of body surface), four intravenous doses of vincristine (1.5 mg/m²), four intravenous doses of daunorubicin (30 mg/m²), and four doses of methotrexate (12 mg/m²) injected into the spine. Doses were calculated and given according to the boy's surface area, which was 0.75 m².

Because of severe complications, the patient was given asparaginase for only six days. Figure 2 diagrams the actual cytotoxic therapy given for 30 days. Figure 1 shows the daily change in several analytes measured during this drug therapy. On day 3 the patient developed acute renal failure.

The phosphate concentration in serum increased to 7.77 mmol/L and ionized calcium decreased severely, to 0.40 mmol/L. The pH was 7.45, serum total calcium 0.77 mmol/L, and serum magnesium 0.66 mmol/L (Figure 1D, F, E, G).

Because of acute symptomatic hypocalcemia with prolonged electrocardiographic QT-interval, the boy was treated with 5-mL doses a 100 g/L solution of calcium levulinate (see Figure 2). Despite the acute change in ionized calcium, the boy had astonishingly few clinical symptoms other than moderate paraesthesia and diminished tendon reflexes.

Monitoring the concentration of ionized calcium, magnesium, and parathyrin indicated hypoparathyroidism. Therefore the therapy with calcium levulinate was stopped and the boy was treated with 1α-hydroxycholecalciferol (0.25 µg three times daily).

Methods. We used an upgraded (4) ICA 1 (Radiometer, Copenhagen, Denmark) to measure ionized calcium in anaerobic capillary whole blood from the child's ear lobe, as previously described (5).

Total calcium and magnesium in serum were measured by atomic absorption spectroscopy (Model 403; Perkin-Elmer Corp., Norwalk, Ct). Parathyrin was measured with a C-terminal parathyrin RIA-kit (Clinical Assays, Immuno-Nuclear Corp., Cambridge, MA). Urate, creatinine, and phosphate were measured in a mechanized analyzer (PRISMA; New Clinicon Corp., Bromma, Sweden).

The arrows indicate that a dose of the drug (see text) was given

Results and Discussion

In the present case of lymphoblastic leukemia the occurrence of acute transient renal failure appears to underlie the various complications, but the biochemical and pathophysiological mechanism of the renal failure is probably complex and multifactorial.

The acute renal failure could be explained on the basis of urate nephropathy. Although allopurinol and sodium bicarbonate were administered to prevent this complication, intensive lysis of lymphoblasts with an increase in serum urate may have precipitated renal nephropathy when cytotoxic therapy was started. Another possible or contributing cause of renal failure in this boy is initial leukemic infiltration of the kidney. The renal insufficiency could explain the severe hyperphosphatemia (Figure 2D), which may have been further aggravated by therapy with a cytotoxic drug and lysis of lymphoblasts, which have four times as much organic and inorganic phosphorus as in mature lymphocytes (6). The hyperphosphatemia may precipitate renal calculi when the solubility product of calcium phosphate is exceeded (7), but roentgenograms revealed no renal calculi or extra-renal deposits of calcium phosphate.

Although the renal function became considerably insufficient (Figure 1C), hemodialysis or peritoneal dialysis was delayed owing to the considerable risk of further complicating the case because of very low leukocyte and thrombocyte count. By conservative treatment the renal function did, however, improve and the concentrations of both phosphate and urate decreased (Figure 1, D and B). The acute renal failure and the hyperphosphatemia both seem to have contributed to the developed acute severe hypocalcemia.

A highly statistical significant linear correlation (r = 0.84, p ≤0.001) was found between actual ionized calcium and the concentration of phosphate during the course of the acute renal failure (Figure 3), indicating that the hypocalcemia was the result of diffuse precipitation of calcium phosphate. The severe hypocalcemia was initially treated with several doses of calcium levulinate (Figure 2), but the hypocalcemia was refractory to this treatment and the parathyrin response seemed to be within the normal reference interval, so the clinical diagnosis of hypoparathyroid-

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Fig. 2. The course of drug therapy in a case of acute leukemia complicated by severe hypocalcemia
The arrows indicate that a dose of the drug (see text) was given

Fig. 3. Correlation between the concentration of ionized calcium (actual value) and phosphate during the course of acute renal failure in this case of leukemia
Regression equation: y = -0.12x + 1.27; r = 0.84

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ism was confirmed, and therapy was converted to proper doses of 1α-hydroxycholecalciferol.

On the basis of these considerations the therapeutic use of calcium salts in the hyperphosphatemic state may have aggravated calcification and renal insufficiency and seems not to have been the optimal choice of therapy (2). The relative hypoparathyroidism, which must have contributed to the persistent hypocalcemia, may be explained by several mechanisms. The hyperphosphatemia may precipitate both hypocalcemia and hypomagnesemia. From in vivo and in vitro studies it is known that hypomagnesemia inhibits the secretion of parathyrin (8). It is also known that a low concentration of magnesium in the plasma would lead to inefficient conversion of adenosine triphosphate to cyclic adenosine monophosphate, diminishing the end-organ response to parathyrin in bone and kidney (9).

Some cytotoxic drugs, such as aminoglycosides, are known to have an inhibitory effect on parathyrin secretion (10), but these drugs were not used in the present case.

Although treatment with asparaginase was eliminated because we supposed it to have caused the unwanted effect of hyperuricemia (Figure 2B), our knowledge of avoidable metabolic disorders ascribable to cytotoxic therapy seems to be limited (1–3).

In conclusion: the present study describes the diagnosis of a severe hypocalcemia and hypoparathyroidism and evaluates the clinical management of this syndrome by longitudinal measurements of ionized calcium during initial cytotoxic treatment of acute leukemia. The basis for this metabolic complication seems to be multifactorial and requires further investigation to adequately prevent and intervene therapeutically to further reduce the morbidity in leukemia.

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References