Editorial Review

Electrolyte and Acid-Base Disturbances in the Management of Leukemia

By Sean O'Regan, Stephen Carson, Russell W. Chesney, and Keith N. Drummond

Leukemia is capable of altering the normal physiologic regulation of many systems, including the serum levels of most electrolytes. It seems probable that the prolonged life expectancy of patients with all forms of leukemia permits more of these electrolyte imbalances to become manifest. The alterations in electrolyte concentration brought on by the leukemic process per se or by the therapeutic measures used have never been reviewed. Such a review is thus timely, since these alterations in electrolyte levels may be life threatening. This report will outline the basic electrolyte and acid-base abnormalities encountered in leukemic patients and discuss some of the theories regarding their pathogenesis.

Sodium

Hyponatremia

Hyponatremia has been infrequently reported in leukemic patients. In one study, hyponatremia developed in 11 of 14 patients with acute myeloblastic and myelomonocytic leukemia. Although the plasma arginine vasopressin levels were entirely appropriate where examined, these patients had hyponatremia with natriuresis and negative free water clearance, findings considered compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Later balance studies done on 42 patients with acute myeloid leukemia confirmed the presence of features of SIADH. Some patients had hyponatremia before any cytotoxic therapy was initiated, and in one patient treated with chlorpropamide, an agent known to induce reversible hyponatremia, the hyponatremia persisted despite discontinuation of the drug. Agents associated with SIADH were not used in these patients. Since cytotoxic therapy increased the magnitude of the hyponatremia and natriuresis, it was suggested that a natriuretic factor was being released from leukemic cells, which was ADH-like in function, but not the native hormone by immunoassay. Hyponatremia with hypocalcemia was observed in two patients—one with chronic lymphocytic leukemia and the other with chronic myelogenous leukemia. No cause was found for these abnormalities. Hyponatremia has also been observed in childhood leukemia in relapse.

Uptake of sodium by leukemic cells could potentially result in hyponatremia.
Studies of intracellular leukocyte cation levels in blast cells from patients with acute lymphoblastic leukemia have demonstrated a relatively lower potassium and higher sodium concentration when compared to normals. A decrease in leukocyte ATPase activity has also been found in chronic lymphatic leukemic cells. However, these differences in leukocyte sodium content and ATPase activity in leukemia were probably related in most cases to technical factors, such as improper cell isolation or failure to allow for differences in volume between normal and leukemic cells. Thus, leukemic cellular sodium uptake does not appear to account for the observed hyponatremia.

Hyponatremia and hypochloremia from SIADH have been described with two cytotoxic agents: vincristine and cyclophosphamide. Hyponatremia associated with vincristine therapy has been seen in childhood leukemia and in acute granulocytic leukemia in adults. Fluid restriction or cessation of therapy with the causative drug reversed this electrolyte abnormality. Impairment of water excretion, with hyponatremia, weight gain, and inappropriately concentrated urine followed high dose (50 mg/kg) parenteral cyclophosphamide therapy in four patients with acute lymphocytic or myeloid leukemia: normal free water clearance returned after discontinuation of therapy.

A spectrum of serum electrolyte abnormalities including hyponatremia and hypochloremia has been reported in febrile leukemic patients undergoing therapy with polymyxin sulfate. Renal tubular toxicity was suggested by increased urine electrolyte excretion in these patients and was related to both duration of therapy and total dose of drug administered.

Diarrhea and vomiting, both frequent complications of chemotherapy, may also result in or intensify hyponatremia.

Hypernatremia

Diabetes insipidus, an infrequent complication of central nervous system leukemia, may lead to hypernatremic dehydration. Postmortem examinations have shown diencephalic and pituitary leukemic infiltrates. Over 20 cases of diabetes insipidus with leukemia have been reported, including three children, one with acute lymphoblastic and two with granulocytic leukemia. Both the hypernatremia and polyuria may respond to vasopressin administration. A potential cause of hypernatremia is the vasopressin-resistant diabetes insipidus associated with hypercalcemia in leukemic patients. However, those case reports of hypercalcemia in leukemia, although emphasizing polyuria, have failed to present the serial serum sodium values which might demonstrate hypernatremia.

POTASSIUM

Hypokalemia

A prominent association between hypokalemia and acute myelogenous leukemia has been repeatedly observed. Its frequency appears so high that all patients with this disease should be observed for this complication and its attendant dangers. The decrease in the serum potassium level is associated with raised serum lysozyme levels. Kaliuresis has been noted
in many of these patients, and has been attributed to renal tubular damage due to massive lysozymuria. However, some have suggested that tubular damage may be responsible for lysozymuria. A similar disturbance occurs in the chloroleukemic rat. Prolonged lysozymuria has appeared to be necessary in causing tubular damage in one animal study, since acute intraaortic perfusion of normal rat kidneys with lysozyme does not induce kaliuresis. However, perfusion of isolated rat kidneys with human lysozyme stimulates excretion of potassium. Recently, the premise that renal damage is the basic pathogenetic factor in the development of hypokalemia in acute myeloid leukemia patients has been challenged. Hypokalemia with metabolic alkalosis in a patient with chronic lymphocytic leukemia has been attributed to the existing kaliuric effect of hypercalcemia. Hypokalemia has also been observed in a child with lactic acidosis and acute lymphoblastic leukemia in relapse.

Acute tubular necrosis and nephrotoxicity have been associated with gentamicin and cephalothin combination therapy. Nine of eleven patients with acute leukemia treated with this antibiotic combination developed hypokalemia; only two showed a rise in serum creatinine levels. Urinary excretion of potassium was extremely high in the one patient in whom it was measured, suggesting that the nephrotoxic effect of the combined antibiotic therapy resulted in severe kaliuresis. Gentamicin therapy of a patient with monocytic leukemia was associated with hypokalemia. Carbenicillin therapy has been associated with the development of hypokalemia, as has prolonged therapy with prednisolone in patients with acute leukemia. Hypokalemia due to polymyxin sulfate nephrotoxicity has been observed in febrile leukemia patients. A retrospective analysis of over 500 serum potassium determinations done in 52 leukemic patients revealed that more than one-third of the patients had at least one episode of mild hypokalemia. The exact cause was not determined. Malnutrition has been suggested as a contributing factor in the hypokalemia seen in childhood leukemia in relapse. Rapid cellular uptake of potassium, as seen in initiation of therapy in B12 deficiency anemia, may also be a factor. Transcellular movement of potassium secondary to antibiotic therapy has been suggested to be a cause of hypokalemia, as may renal potassium excretion due to a nonabsorbable anion effect of antibiotic therapy.

Hyperkalemia

Hyperkalemia is an infrequently documented complication in leukemia. It appears to occur with massive lysis of neoplastic cells after initiation of induction therapy. Irradiation of the spleen in a case of chronic lymphatic leukemia has also resulted in hyperkalemia. Hyperkalemia due to urate nephropathy has been noted following L-asparaginase therapy, and with acute renal failure and acidosis following vincristine and prednisone therapy. Acute monocytic leukemia presenting with uric acid nephropathy and hyperkalemia has also been described. In general, therefore, hyperkalemia is observed as a complication of cytotoxic therapy due to rapid cell lysis or acute renal failure secondary to hyperuricemia. The possibility that hyperkalemia is due to potassium release from cell lysis is strengthened by the observation that the potassium concentration of...
lymphocytes from patients with chronic lymphatic leukemia is increased. Two instances of sudden death of patients with chronic lymphocytic leukemia have been attributed to hyperkalemia. 

Irradiation of the spleen in patients with chronic monocytic leukemia and chronic lymphatic leukemia has resulted in increased urinary excretion of potassium; serial serum potassium levels were not done on these patients.

Plasma from patients with leukemia may have falsely high potassium levels because of breakdown of leukocytes or platelets between the time of venipuncture and separation of the serum or plasma. This finding is termed "spurious" or pseudohyperkalemia, and has been seen in acute lymphatic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. In many of the patients whose serum potassium values were falsely high, the peripheral white cell counts were also elevated. Hyperkalemia was associated with high leukocyte smear or smudge cell count, the latter possibly due to increased leukocyte fragility. The phenomenon has been reported in clotted blood and in heparinized samples. Therefore, hyperkalemia in leukemic patients in the absence of appropriate clinical and EKG abnormalities, especially if there is a high peripheral white cell count, should raise suspicion that cellular lysis may be the pathogenetic factor. This in vitro phenomenon is of no clinical significance except that it must be distinguished from true hyperkalemia so that inappropriate overtreatment can be avoided.

CALCIUM

Hypocalcemia

Hypocalcemia is commonly seen in leukemia, and may usually be ascribed to either uremia or hypoalbuminemia. Hypocalcemia, hyperphosphatemia, and hyperphosphaturia were found in 4 of 14 children. These four had high peripheral lymphoblast counts and some evidence of renal insufficiency. Hypocalcemia was felt to be secondary to hyperphosphatemia, resulting from phosphate release after cell lysis due to initiation of chemotherapy. A similar phenomenon has been observed in a patient with chronic lymphocytic leukemia, in two patients with acute myeloid leukemia, and a child with acute lymphoblastic leukemia. A retrospective study of over 500 serum calcium determinations in patients with acute leukemia indicated that one-third of the patients had constant, and almost half had intermittent hypocalcemia. Prior treatment with antibiotics and glucocorticoids were believed to be contributory pathogenetic factors. In a review of 323 cases of leukemia, 19 patients had hypocalcemia. Fifteen had evidence of uremia or hypoalbuminemia. Three cases of chronic myeloid leukemia and one of chronic lymphatic leukemia had low serum protein levels. Sixteen episodes of hypocalcemia were detected in 14 of 135 children hospitalized for acute leukemia. Renal failure was responsible for five episodes. However, no common etiologic factor could be found to explain the other episodes. Hypocalcemia has occasionally been seen in gram-negative sepsis, and this may be an etiologic factor in some cases. Malnutrition, steroid therapy, and interference with 25-hydroxylation of vitamin D have also been discussed as possible etiologic factors. A readily reversible form of hypocalcemia was seen in one adult with chronic monocytic leukemia on busulfan therapy; calcium gluconate administration...
corrected this imbalance. Another patient with chronic monocytic leukemia who had no evidence of renal disease developed hypocalcemia while in relapse. Other drugs, such as polymyxin B and L-asparaginase, have been associated with hypocalcemia. Hypocalcemia with excessive urinary excretion of calcium was found in 18 patients receiving polymyxin B; it was suggested that this drug led to a dose- and time-related degree of renal tubular damage, although the precise site of tubular damage is unknown. Hypocalcemia, hyperphosphatemia, and hyperphosphaturia have followed treatment with L-asparaginase, a drug which in rabbits has a direct toxic action on the chief cells of the parathyroid glands. Though a similar mechanism may be operative in humans, hypocalcemia has appeared to be due to hypoalbuminemia induced by the drug. L-asparaginase-induced hypocalcemia with tetany has been reported in a leukemic child. Therapy with 6-mercaptopurine was also suggested as a cause for hypocalcemia in leukemia. Hypocalcemia secondary to hypomagnesemia has been described in a case of myelogenous leukemia. The hypomagnesemia was attributed to gentamicin therapy.

**Hypercalcemia**

Hypercalcemia is being recognized with increasing frequency in both adults and children with all forms of leukemia. Hypercalcemia has even been described in canine leukemia. Eighty-six cases with leukemia and hypercalcemia have been described since 1936. In two retrospective series, the incidence of hypercalcemia in all types of leukemia was about 2.5%. Although hypercalcemia is more common in acute lymphatic leukemia, it has been found in acute myeloid, chronic lymphocytic, chronic myelogenous, and in undifferentiated leukemia.

Several theories have been proposed to explain the development of hypercalcemia in leukemic patients. However, in few instances has a satisfactory explanation been discovered. Necropsy examination has not shown parathyroid gland hypertrophy. In two cases, infiltration of the parathyroid glands has been observed. It was suggested that in one patient the leukemic cell infiltration resulted in excess parathormone (PTH) release. Administration of exogenous PTH to this patient did not result in a phosphaturic response. The authors suggested that maximal PTH stimulation was preexisting. One patient with chronic lymphocytic leukemia was found to have a single parathyroid adenoma. Surgical removal of the adenoma resulted in resolution of the hypercalcemia. Hyperresponsiveness to normal PTH levels has not been evaluated. Where serum PTH levels have been measured, they have generally been normal. The percentage of renal tubular reabsorption of phosphate has also been normal. Most of these cases have been in adults, but some reported were in children.

The clinical presentation of patients with leukemia complicated by hypercalcemia is varied. They may present with lethargy, nausea, vomiting, and epigastric pain, or marked polyuria, the latter being a consequence of loss of the normal renal concentrating ability due to the hypercalcemia. Occasionally, the symptoms of hypercalcemia may be the presenting feature of leukemia. Leukemic cells may not be present in peripheral blood smears,
and a bone marrow examination is often necessary to make the diagnosis. Many of these patients are azotemic and have other features of renal insufficiency; nephrocalcinosis is commonly found on necropsy.

Three reports in children ascribed the hypercalcemia to the production of a PTH-like substance by leukemic tissue. Antileukemic therapy in two of these patients resulted in resolution of the hypercalcemia. In one child with acute lymphatic leukemia, the combination of prednisone, daunorubicin, and vincristine led to increased serum phosphate levels and decreased urine phosphate excretion; the other patient had resolution of hypercalcemia following antileukemic therapy. Another report described a boy with acute lymphatic leukemia and hypercalcemia who had markedly increased serum PTH levels by radioimmunoassay. He died of sepsis while leukopenic, and had normal size parathyroid glands on necropsy. The authors suggested that the hypercalcemia resulted from a PTH-like substance secreted by leukemic cells. Hypercalcemia in a man with acute myelogenous leukemia was associated with increased serum PTH levels. In vitro studies on the patient’s myeloblasts suggested the malignant cells as the source of excess PTH.

Hypercalcemia was described in a patient with chronic myeloid leukemia whose lesion had progressed to myelofibrosis and massive bony erosion. Another patient had acute myelomonocytic leukemia, monoclonal macroglobulinemia, Bence Jones proteinuria, and hypercalcemia; this patient had bone pain and extensive involvement of the marrow, but serum phosphorus was consistently decreased, and the authors speculated that blast cells were synthesizing a polypeptide with PTH-like activity.

Many authors have ascribed the hypercalcemia to bone infiltration by leukemic cells. Most leukemic patients with hypercalcemia have abnormal skeletal radiographs; however, the incidence of skeletal changes in leukemia is as high as 30%, making a direct cause-effect relationship difficult to assess. Nies and associates have found radiologic evidence of bone lesions in 11% of 316 patients who died of acute leukemia and found no consistent changes in serum calcium from the control group. Bone disease in leukemic patients appears to be much more common than hypercalcemia. The presence of leukemic tissue contiguous with bone spicules suggests that leukemic infiltration of bone may be instrumental in inducing hypercalcemia. Several authors have suggested that the presence of an osteolytic sterol or prostaglandin secretion may be responsible for hypercalcemia in leukemia. A group of osteoclast-activating factors have been found in the supernatant of cultured leukocytes. These may lead to bone destruction and hypercalcemia in some patients with multiple myeloma and Burkitt’s lymphoma, but cells grown from leukemic patients have not been shown to have any bone-resolving activity. Hypersensitivity to vitamin D is unlikely in view of the poor calcium lowering response to corticosteroids in some of these patients. Regardless of the cause of hypercalcemia, it is the most commonly reported electrolyte abnormality in leukemia.

The presence of hypercalcemia indicates a grave immediate prognosis. Canellos’ comments that the median survival period of 22 hypercalcemic leukemia patients reported in various series was 3 mo in acute leukemia of any type, and 15 days in those with chronic granulocytic leukemia. The latter patients all were in an accelerated phase of their disease. The poor prognosis
of these patients suggests that therapy directed at lowering the serum calcium levels has been only moderately successful in influencing the time course of their disease. Measures used to control hypercalcemia in leukemic patients have included administration of oral phosphate, intravenous sodium phosphate, sodium sulfate, steroids, furosemide, and increased fluid intake; peritoneal and hemodialysis have also been used. These measures have been of limited value and have lowered serum calcium levels only temporarily. The most effective therapy has been the use of cytotoxic agents directed at the leukemic process itself. However, occasionally, steroids have proved effective.

PHOSPHATE

Hyper- and Hypophosphatemias

Most abnormalities of serum phosphate levels have been associated with abnormal serum calcium levels. Hyperphosphatemias may follow rapid lysis of leukemic cells after initiation of chemotherapy. Jordan has found that 18% of 123 cases of leukemia in whom renal function has been normal had hyperphosphatemia which he felt was related to rapid osteolysis. Hypophosphatemia has been noted in association with hypocalcemia in 2% of Jordan’s cases, and in eight children with hypokalemia. Phosphate depletion with hypophosphatemia, hypophosphaturia, and depressed erythrocyte ATP levels were found in a patient with lymphoblastic leukemia who was habituated to an antacid preparation containing calcium carbonate known to decrease phosphate absorption. Both this patient and another hypophosphatemic patient developed hyperphosphatemia with a striking increase in urine phosphate excretion after the administration of cytotoxic therapy. It was postulated that cellular uptake of phosphate by blast cells led to this hypophosphatemia, and to hyperphosphatemia following cell lysis.

In general, therefore, abnormalities of serum phosphate levels are associated with abnormal serum calcium levels.

MAGNESIUM

Hyper- and Hypomagnesemia

It is difficult to draw any conclusions about the significance of serum magnesium levels in leukemia. Plasma levels of magnesium appear to depend on nutritional status, drug therapy, and type of leukemia. Elevated magnesium levels have been observed in the plasma of patients with chronic lymphatic leukemia and chronic myeloid leukemia. Normal serum values have also been reported in chronic lymphatic leukemia. However, others have reported an increase in urinary magnesium excretion in the presence of normal serum values in patients with chronic lymphatic leukemia. Acute lymphoid leukemia in one patient has been associated with a raised plasma magnesium level. A significant increase in mean serum magnesium levels has been observed in 22 patients with leukemia during treatment, suggesting that magnesium, the second most abundant intracellular cation, is being released from damaged malignant cells. In two patients, serum magnesium levels in the cardiotoxic range have been observed. Hypermagnesemia has also been observed in acute leukemia in children in relapse.
Normal mean plasma magnesium levels have been seen in acute myeloblastic leukemia in relapse. In acute leukemia of childhood, hypomagnesemia was observed in association with hypocalcemia in two patients. Administration of magnesium sulfate was required to correct the hypomagnesemia and hypocalcemia. Hypomagnesemia attributed to gentamicin therapy has been seen in a woman with monocytic leukemia. Hypomagnesemia has also been reported in acute leukemia in relapse. In the latter study, poor nutritional status and excessive weight loss appeared to be responsible for the low values recorded.

**ACID-BASE DISTURBANCES**

Metabolic alkalosis has been observed in leukemia in association with hypercalcemia. Metabolic alkalosis is seen in hypercalcemia from other causes, often in conjunction with hypokalemia, and may be due to intravascular volume depletion secondary to polyuria and renal potassium wasting. These patients develop a vasopressin-resistant diabetes insipidus. Metabolic alkalosis associated with hypokalemia has been observed in children with acute leukemia in relapse; this resolved following potassium chloride supplementation. Alkalosis and acidosis have also been seen in association with hypocalcemia in childhood leukemia.

Hypouricemia with aminoaciduria and hyperphosphaturia—evidence of proximal tubular dysfunction—has been found in two patients with acute myelogenous leukemia. Pyrazinamide, an agent which blocks tubule urate secretion, did not suppress urinary urate secretion. One of these patients had evidence of renal tubular acidosis. Other patients with acute myeloid leukemia were found to have aminoaciduria, suggesting some form of tubular dysfunction.

Severe lactic acidosis has been described in patients with acute lymphoblastic or myeloblastic leukemia. This situation has also been seen in chickens with avian myeloblastosis. Many of these leukemic patients have developed lactic acidosis during episodes of shock or pulmonary edema; however, most did not have obvious hypoxia. It has been suggested that the acidosis may be due to deranged carbohydrate metabolism, resulting from a decrease in liver glucose-6-phosphatase content in leukemic patients. Lactic acidosis has only been seen in patients in relapse, has been most prominent in those with massive leukemic infiltrates, and has resolved with the institution of therapy to induce remission. Anaerobic production of lactic acid by masses of leukemic cells packed into organs may explain the lactic acidosis seen in these patients. Elevated leukocyte counts can increase whole blood viscosity, since leukemic white cells are not as readily deformable as red cells; thus, microvascular aggregates could form, which might lead to poorly perfused tissues with resultant hypoxemia. A shift to lactate production might then ensue, leading to lactic acidosis. In vitro studies indicate that lactate production by leukemic cells is sufficient to produce acidosis in the absence of hypoxia. Bicarbonate therapy has been of benefit in the treatment of lactic acidosis in leukemia.

Though hyperglycemia is a frequent complication of L-asparaginase therapy, only rarely has diabetic ketoacidosis been observed. Concomitant steroid
therapy appears to potentiate the hyperglycemic effects of the L-asparaginase. Insulin has been required for therapy of the ketoacidosis.5136

SUMMARY

Electrolyte disturbances in leukemia can be the result of the disease process or drug therapy. One group of electrolyte abnormalities is related to the stage of the leukemic process. Included in this group are newly diagnosed patients who may show elevated serum potassium, phosphorus, and magnesium—a result of their release from malignant cells after cytotoxic therapy or their accumulation due to urate nephropathy. Patients in remission usually have normal serum electrolyte concentrations, but acute leukemia patients during relapse may have hypokalemia, hypophosphatemia, and hypomagnesemia. This imbalance may be related to cellular uptake of these electrolytes in the presence of inadequate dietary intake. Other factors contributing to electrolyte derangements, and related to the leukemic process, include hyponatremia and hypochloremia secondary to the SIADH, hypokalemia in acute monocytic or acute myelomonocytic leukemia due to lysozyme-induced tubular damage, hypercalcemia possibly secondary to leukemic infiltration of bone or parathyroid glands (with PTH release), or production of a PTH-like substance by leukemic cells. Nonspecific factors related to the disease process which may aggravate the electrolyte imbalance include gastrointestinal loss through nausea, vomiting, and malnutrition.

The drug-related electrolyte abnormalities include cyclophosphamide- and vincristine-induced SIADH; decreased serum sodium, chloride, potassium, and calcium concentrations as a result of polymyxin B nephrotoxicity; hypokalemia and hypomagnesemia secondary to amphotericin B; hypocalcemia, hypophosphatemia, and hyperphosphaturia due to L-asparaginase-induced hypoparathyroidism; hypokalemia due to a nonreabsorbable anion effect of antibiotics in the distal tubule or changes in membrane ionic transport of all cells by large doses of antibiotics.

Electrolyte disturbance in leukemia thus have a multifactorial pathogenesis which can best be delineated according to the stage of the leukemic process and the drugs being used. Recognition of the cause or causes in a particular patient is essential for an effective approach to management. This review emphasizes the need for routine measurement of serum electrolytes during all phases of the leukemic process.

Editor’s Note: The authors have prepared an exhaustive list of 148 references. In order to conserve space, the references have not been published with the paper, but may be obtained alone or with reprints requested from Dr. O’Regan.
Electrolyte and acid-base disturbances in the management of leukemia

S O'Regan, S Carson, RW Chesney and KN Drummond