

Acid–Base and Electrolyte Abnormalities in Patients With Acute Leukemia

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Disturbances of acid–base balance and electrolyte abnormalities are commonly seen in patients with acute leukemia. Our study aimed at illuminating the probable pathogenetic mechanisms responsible for these disturbances in patients with acute leukemia admitted to our hospital. We studied 66 patients (24 men and 44 women) aged between 17 and 87 years old on their admission and prior to any therapeutic intervention. Patients with diabetes mellitus, acute or chronic renal failure, hepatic failure, patients receiving drugs that influence acid–base status and electrolyte parameters during the last month, such as corticosteroids, cisplatin, diuretics, antacids, aminoglycosides, amphotericin, penicillin, and K^+ , PO_4^{3-} , or Mg^{2+} supplements were excluded. Forty-one patients had at least one acid–base or electrolyte disturbance. There were no significant differences in the incidence of acid–base balance and electrolyte abnormalities between patients with acute myeloid leukemia (AML) and patients with acute lymphoblastic leukemia (ALL). The most frequent electrolyte abnormality was hypokalemia, observed in 41 patients (63%), namely in 34 patients with AML, and 7 with ALL; the main underlying pathophysiologic mechanism was inappropriate kaliuresis. Furthermore, hypokalemic patients more frequently experienced concurrent electrolyte disturbances (i.e., hyponatremia, hypocalcemia, hypophosphatemia, and hypomagnesemia), as well as various acid–base abnormalities compared to normokalemic patients. Hypokalemia in patients with acute leukemia may serve as an indicator of multiple concurrent, interrelated electrolyte disturbances, especially in patients with AML. *Am. J. Hematol.* 62:201–207, 1999. © 1999 Wiley-Liss, Inc.

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INTRODUCTION

Disturbances of acid–base balance and electrolyte abnormalities are commonly seen in patients with acute leukemia, due to either leukemic processes, organ infiltration, and cell death or to adverse effects of cytotoxic drugs [1,2]. Among these metabolic perturbations, hypokalemia appears to be the most frequent [3,4]. However, detailed analysis of these abnormalities and their interrelations in leukemic patients is lacking. We undertook the present study in order to illuminate the pathophysiologic mechanisms responsible for the development of acid–base and electrolyte disorders in patients with acute leukemia admitted to our hospital.

MATERIAL AND METHODS

A total of 66 patients with acute leukemia, aged 17–87 years (24 males and 42 females) hospitalized in our clinic

were studied. Fifty-four patients had acute myeloid leukemia (AML), and 12 patients had acute lymphoblastic leukemia (ALL). On histologic examination, AML patients were classified as M1 ($n = 6$), M2 ($n = 9$), M3 ($n = 7$), M4 ($n = 17$), and M5 ($n = 15$). Two patients (16.7%) had T-cell leukemia and ten patients had B-cell leukemia. Twenty-seven AML patients and seven ALL patients were included in the study on first diagnosis. Thirteen AML patients and one ALL patient were included after relapsing. Two out of these 13 AML patients experienced their second relapse. Fourteen AML patients and four ALL patients were at disease remission follow-

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ing intensive chemotherapy. In treated patients the average time between therapeutic interventions and blood and urine sampling was 2 weeks.

Forty-two patients (out of the total 66) were admitted because of various emergencies: i.c. fever with or without sore throat ($N = 26$), and refractory gastrointestinal complaints [vomiting ($N = 9$) or diarrhea ($N = 7$)]. Of these 42 patients, 13 patients were newly diagnosed, 8 suffered a disease relapse, and 15 were readmitted after having completed the remission induction phase. Furthermore, six patients were recovering from aplasia (neutrophil count 900–1400 mm^{-3} , platelet count 8,000–33,000 mm^{-3}) following remission induction ($N = 4$) and consolidation therapy ($N = 2$).

Patients with diabetes mellitus, acute or chronic renal failure, hepatic failure, patients receiving drugs that influence acid–base status and electrolyte parameters during the last month, such as corticosteroids, cisplatin, diuretics, antacids, aminoglycosides, amphotericin, penicillin, and K^+ , PO_4^{3-} , or Mg^{2+} supplements were excluded. Upon their admission and prior to any therapeutic intervention, venous blood was drawn for the determination of serum glucose, urea, creatinine, total proteins, albumin, K^+ , Na^+ , Ca^{2+} , PO_4^{3-} , Cl^- , Mg^{2+} , and HCO_3^- . To avoid the transfer of electrolytes into metabolically active leukemic cells, we separated the blood from cells rapidly. Serum osmolality (P_{osm}) was measured by vapor-action osmometer and arterial blood was obtained for blood gases measurements. In patients with hypoalbuminemia (serum albumin < 40 g/l) corrected serum Mg^{2+} was calculated using the formula: corrected Mg^{2+} (mmol/l) = measured Mg^{2+} (mmol/l) + 0.005 \times (40 – albumin g/l) [5]. Moreover, the corrected for the degree of hypoalbuminemia serum Ca^{2+} was calculated by adding 0.2 mmol/l to the total serum Ca^{2+} concentration for every 10 g/l decrement in serum albumin from normal value (assumed to be 40 g/l) [6]. Serum anion gap (SAG) was calculated from the equation: $\text{SAG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ [7]. Additionally, in cases of increased SAG the presence of a mixed acid–base disorder was tested by determining the $\Delta\text{AG}/\Delta\text{HCO}_3^-$ ratio, which in cases of isolated (pure) high SAG metabolic acidosis is between 1 and 2 [8].

At the same time fresh urine specimen was tested for osmolality (U_{osm}), creatinine, K^+ , Na^+ , Ca^{2+} , PO_4^{3-} , Cl^- , Mg^{2+} .

In hyponatremic patients the fractional excretion of Na^+ (FENa^+) was calculated from the equation: FENa^+ (%) = (urine $\text{Na}^+ \times$ serum creatinine) \times 100/(serum $\text{Na}^+ \times$ urine creatinine). A fractional excretion of less than 0.1% was considered as indicative of hypovolemia [9].

In hypokalemic patients the fractional excretion of K^+ (FEK^+) was calculated from the equation FEK^+ (%) = (urine $\text{K}^+ \times$ serum creatinine) \times 100/(serum $\text{K}^+ \times$ urine creatinine), and the transtubular K^+ gradient (TTKG) was

TABLE I. Urinalysis Results

Disturbance	AML patients	ALL patients
Proteinuria ^a (>1+)	6	0
Pyuria ^b	6	1
Microscopic hematuria ^c	15 (2)	2 (0)
Granular casts	13	0

^a24 h urine protein concentration >150 mg (180–310 mg).

^bMore than 3 leukocytes per high-power field in the absence of positive urine cultures.

^cMore than 3 erythrocytes per high-power field. In parentheses, number of patients with severe thrombocytopenia (platelets $< 10,000/\text{mm}^3$).

calculated from the equation $\text{TTKG} = [\text{urine } \text{K}^+ / (U_{\text{osm}} / P_{\text{osm}})] / \text{serum } \text{K}^+$. A fractional excretion of more than 6.4%, as well as a TTKG greater than 2 were considered as inappropriate kaliuresis in hypokalemic patients [10–12].

In hypomagnesemic patients the fractional excretion of Mg^{2+} (FEMg^{2+}) was calculated from the equation FEMg^{2+} (%) = (urine $\text{Mg}^{2+} \times$ serum creatinine) \times 100/(serum $\text{Mg}^{2+} \times$ urine creatinine). A value more than 4% was considered indicative of inappropriate Mg^{2+} loss in the urine [13].

The fractional excretion of PO_4^{3-} (FEPO_4^{3-}) in patients with hypophosphatemia was calculated from the equation FEPO_4^{3-} (%) = (urine $\text{PO}_4^{3-} \times$ serum creatinine) \times 100/(serum $\text{PO}_4^{3-} \times$ urine creatinine). A fractional excretion of more than 20% was considered as inappropriate [14]. The renal tubular threshold concentration for PO_4^{3-} ($\text{TmPO}_4^{3-}/\text{glomerular filtration rate}$) was determined by the nomogram of Walton and Bijvoet [15].

Urinalysis (including microscopy), and 24 h urinary protein determination were performed in all patients upon admission.

Statistical analysis was performed by χ^2 test. Linear regression analysis was used for the correlation between parameters. For non-normally distributed parameters (i.e., pH) logarithmically transformed values were used for regression analysis. The significance level was set at 0.05.

RESULTS

Urinalysis (including microscopy) results, shown in Table I, revealed that microscopic hematuria was the most common finding, even though patients with severe thrombocytopenia (platelets $< 10,000/\text{mm}^3$) were excluded. Granular casts, pyuria, and proteinuria were also evident in the urine examination of patients with electrolyte disturbances. Finally, uric acid and phosphate crystals were also occasionally found in 9 and 4 patients, respectively.

The acid–base and electrolyte abnormalities of the study population are shown in Table II. Forty-one pa-

TABLE II. Acid-Base Disturbances and Electrolyte Abnormalities in Patients With Acute Myelogenous Leukemia (AML) vs Acute Lymphoblastic Leukemia (ALL)

	AML patients (N = 54)	ALL patients (N = 12)	P
<u>Electrolyte abnormalities</u>			
Hypokalemia (serum potassium <3.5 mmol/l, range 2.5–3.3 mmol/l)	34/54 (63%)	7/12 (58.3%)	NS
Hyponatremia (serum sodium <135 mmol/l, range 131–134 mmol/l)	5/54 (9.3%)	1/12 (8.3%)	NS
Hypomagnesemia (corrected serum magnesium <0.65 mmol/l, range 0.47–0.61 mmol/l)	17/54 (31.5%)	3/12 (25%)	NS
Hypophosphatemia (serum phosphorus <2.5 mg/dl, range 1.6–2.3 mg/dl)	19/54 (35.2%)	2/12 (16.6%)	NS
Hypocalcemia (serum calcium <8.4 mg/dl, range 5.7–8.2 mg/dl)	28/54 (51.9%)	2/12 (16.6%)	<0.05
<u>Acid-base disturbances</u>			
Pure respiratory alkalosis	2/54	1/12	NS
Pure metabolic alkalosis	3/54	1/12	NS
Mixed respiratory alkalosis and metabolic alkalosis	2/54	–	NS
Normochloremic metabolic acidosis and respiratory alkalosis	3/54	1/12	NS
Hyperchloremic metabolic acidosis and respiratory alkalosis	2/54	–	NS
Mixed metabolic alkalosis and respiratory acidosis	2/54	–	NS

tients had at least one acid-base disorder or electrolyte disturbance. Hypokalemia was the most frequent electrolyte abnormality observed in 41 patients (63%). All hypokalemic patients had evidence of renal K^+ wasting ($FEK^+ > 6.4\%$, $TTKG > 2$), while serum K^+ levels were inversely correlated with both FEK^+ ($r = -0.65$, $p = 0.0001$) and $TTKG$ ($R = -0.55$, $P = 0.001$). Eighteen hypokalemic patients experienced severe hypomagnesemia (serum $Mg^{2+} < 0.55$ mmol/l), while serum K^+ levels were correlated with serum Mg^{2+} levels ($R = 0.36$, $P = 0.02$). Thirteen hypokalemic patients had at least one abnormal finding in the urine examination (13 had microscopic hematuria, 6 proteinuria, 6 pyuria, and 10 had urinary casts). Three hypokalemic patients also had a history of diarrhea, and nine had alkalemia. However, no correlation between serum K^+ levels and total leukocyte count or arterial pH was observed. It should be mentioned that the incidence of hypokalemia was higher in patients with acute monocytic and acute myelomonocytic leukemia compared to those of the other AML groups (81.2% vs 27.2%, $P = 0.0001$).

Hyponatremia was found in 6 patients (9%). Four of these patients were hypovolemic, with a urea/creatinine ratio greater than 40 and a $FENa^+ < 0.1\%$ (two patients presented with vomiting, one with diarrhea, and one with both diarrhea and vomiting). Two patients exhibited hyponatremia with inappropriate natriuresis ($FENa^+ > 3\%$). One of them fulfilled the criteria for the diagnosis of the syndrome of inappropriate antidiuresis [16], while in the second patient [who had a slight increase in serum creatinine (i.e., 1.6 mg/dl), abnormal findings in the urine examination (granular casts), clinical as well as laboratory evidence of extracellular volume depletion], the diagnosis of the so-called renal salt wasting syndrome was established. It should be mentioned that in hyponatremic patients there was no evidence of underlying infection.

Hypomagnesemia was seen in 20 (30.3%) patients. Eight of these patients had inappropriate magnesuria

($FEMg^{2+} > 4\%$), partly related to the coexistent metabolic acidosis (3 patients), and hypophosphatemia (7 patients). Additionally, in 5 patients with hypomagnesemia and renal Mg^{2+} wasting there were abnormal findings in the urine examination including urinary casts (5 patients), proteinuria (2 patients), pyuria (2 patients), and microscopic hematuria (4 patients). Of the remaining 12 patients, 4 had alkalemia, and 3 had a history of diarrhea. Serum Mg^{2+} levels were not correlated with total leukocyte count, arterial pH, serum PO_4^{3-} levels or $FEMg^{2+}$.

Twenty-one patients (31.8%) had hypophosphatemia. Of these, 11 had also significant phosphaturia ($FEPO_4^{3-} > 20\%$, $TmPO_4^{3-}/GFR < 2.7$ mg/dl), possibly due to the coexistent hypomagnesemia (five patients), and metabolic acidosis (two patients). The remaining four hypophosphatemic patients with inappropriate phosphaturia exhibited abnormal findings in the urinary examination (urinary casts, microscopic hematuria, as well as phosphate crystals). Two hypophosphatemic patients had a chronic diarrheal syndrome, while three exhibited respiratory alkalosis. Interestingly, an inverse correlation between serum PO_4^{3-} levels and $FEPO_4^{3-}$ ($R = -0.47$, $P = 0.0001$) was observed, while a positive correlation ($R = 0.40$, $P = 0.01$) between serum K^+ and PO_4^{3-} levels was evident. However, serum PO_4^{3-} levels were not correlated with total leukocyte count, arterial pH or serum Mg^{2+} levels.

Thirty patients (45.4%) had hypocalcemia. However, only 13 hypocalcemic patients (19.7%) had true hypocalcemia (12 with AML and 1 with ALL), when the corrected for the degree of hypoalbuminemia serum Ca^{2+} concentration was calculated (serum Ca^{2+} 6.2–8.2 mg/dl). Eight of the 13 hypocalcemic patients had also hypomagnesemia, and 3 more had primary respiratory alkalosis and increased calciuria ($FECa^{2+} > 3\%$). Bacteremia was proved in three febrile hypocalcemic patients (2 of whom had also hypomagnesemia), while 2 patients had GI tract losses. Serum Ca^{2+} levels were well corre-

TABLE IIIA. Electrolyte Abnormalities and Acid–Base Disturbances in Hypokalemic vs Normokalemic Patients With Acute Leukemia

Abnormality	Hypokalemic patients (N = 41)	Normokalemic patients (N = 25)	P
<u>Electrolyte abnormalities</u>			
Hyponatremia	6/41 (14.6%)	0/25 (0%)	NS
Hypocalcemia	28/41 (68.3%)	2/25 (8%)	<0.001
Hypophosphatemia	18/41 (44%)	3/25 (12%)	<0.01
Hypomagnesemia	18/41 (44%)	2/25 (8%)	<0.01
<u>Acid–base disturbances</u>	17/41 (41%)	0/25 (0%)	<0.005

lated with serum Mg^{2+} levels ($R = 0.57$, $P = 0.001$), arterial pH ($R = -0.26$, $P = 0.029$), and serum K^+ levels ($R = 0.65$, $P = 0.001$). In addition to the 3 patients with respiratory alkalosis, 4 more hypocalcemic patients exhibited increased calciuria, while serum Ca^{2+} levels were inversely correlated with $FECa^{2+}$ ($R = -0.38$, $P = 0.01$). Among these 4 patients, three had low serum PO_4^{3-} levels, and 2 had abnormal findings in the urinary examination (proteinuria, granular casts).

Seventeen out of 66 patients had acid–base disturbances (Tables II and III). Specifically, three patients (4.5%) had primary respiratory alkalosis with a mean arterial pH of 7.48 (range 7.47–7.49), a mean pCO_2 of 32 mmHg (range 30–35 mmHg), and a mean HCO_3^- concentration of 21 mmol/l (range 19–22 mmol/L). All three patients exhibited severe hypoxemia ($pO_2 < 60$ mmHg).

Four patients (6%) exhibited pure metabolic alkalosis (mainly owing to upper gastrointestinal fluid loss) with a mean arterial pH of 7.48 (range 7.47–7.50), a mean pCO_2 of 46 mmHg (range 44–48 mmHg), and a mean HCO_3^- concentration of 29 mmol/l (range 28–30 mmol/l). These patients were severely hypokalemic (serum K^+ levels between 2.5 and 2.7 mmol/l), and hypovolemic [increased serum urea/creatinine ratio and decreased urine Cl^- concentration (<20 mmol/l)].

Two patients (3%) had mixed respiratory and metabolic alkalosis. Both patients displayed hypoxemia (pO_2 : 55 and 58 mmHg, respectively), hypovolemia, and hypokalemia (serum K^+ 2.6 and 2.7 mmol/l). Arterial pH was 7.51 and 7.56, pCO_2 34.5 and 33 mmHg, and HCO_3^- concentration 27 and 29 mmol/l, respectively.

Six patients (9%) experienced a primary metabolic acidosis coexisting with a primary respiratory alkalosis. Four of these patients (6%) had a primary normochloremic (wide-gap) metabolic acidosis in concurrence with a primary respiratory alkalosis, defined by a measured pCO_2 less than the predicted by Albert's formula (17) [expected arterial carbon dioxide tension = $1.5 \times$ (serum HCO_3^-) + 8 ± 2]. These patients had also a decreased $\Delta AG/\Delta HCO_3^-$ ratio, as the decrease in serum HCO_3^- concentration was significantly higher than the increase in SAG. Underlying infection was highly suspected on

TABLE IIIB. Electrolyte Abnormalities and Acid–Base Disturbances in Patients With Marked Hypokalemia (Serum Potassium <2.8 mmol/l) vs Patients With Mild Hypokalemia (Serum Potassium 2.8–3.3 mmol/l)

Abnormality	Patients with marked hypokalemia (N = 19)	Patients with mild hypokalemia (N = 22)	P
<u>Electrolyte abnormalities</u>			
Hyponatremia	2/19 (10.5%)	4/22 (18.2%)	NS
Hypocalcemia	14/19 (73.7%)	14/22 (63.6%)	NS
Hypophosphatemia	15/19 (79%)	3/22 (13.6%)	0.01
Hypomagnesemia	14/19 (73.7%)	4/22 (18.2%)	0.01
<u>Acid–base disturbances</u>	12/19 (63.1%)	5/22 (22.7%)	0.01

admission. Blood cultures were positive for *Escherichia coli* in three patients and *Klebsiella pneumoniae* in one case. Arterial pH was between 7.32 and 7.34, pCO_2 between 28 and 32 mmHg, and HCO_3^- concentration between 19 and 21 mmol/l. SAG ranged between 19 and 21 mmol/l, while the $\Delta AG/\Delta HCO_3^-$ ratio was close to 2. The remaining two patients (3%) had a primary hyperchloremic metabolic acidosis coexisting with a primary respiratory alkalosis, a disturbance detected by a measured pCO_2 less than that predicted by the formula of Albert et al. [17]. On admission, both patients complained of acute onset diarrhea, and *Salmonella enteritidis* was isolated in stool cultures in both cases. Arterial pH was 7.34 and 7.32, pCO_2 29 and 32 mmHg, pO_2 56 and 53 mmHg, serum HCO_3^- concentration 19 and 20 mmol/l, SAG 8 and 9 mmol/l, and serum Cl^- concentration 107 and 109 mmol/l, respectively.

Two patients (3%) had a primary metabolic alkalosis combined with a primary respiratory acidosis. This mixed acid–base disorder was diagnosed by a measured pCO_2 more than that predicted by the respiratory compensation of metabolic alkalosis (increase of pCO_2 by 0.6–0.7 mmHg for each 1 mmol/l increase in HCO_3^- concentration). Serum K^+ concentration was 2.6 and 2.8 mmol/l, respectively. On admission, lower respiratory infection was clinically and radiologically evident, and in one case pneumococcus was isolated from blood cultures. Arterial pH was 7.47 and 7.48, pCO_2 49 and 50 mmHg, and HCO_3^- concentration was 34 and 36 mmol/L, respectively.

There were no significant differences in the incidence of electrolyte abnormalities and acid–base equilibrium disturbances between patients with AML and ALL, except for hypocalcemia, which was more frequently observed in AML patients (Table II). It is worth mentioning that concurrent acid–base and electrolyte abnormalities were evident mainly in patients with acute leukemia and hypokalemia. In fact, as shown in Table IIIA, the incidence of electrolyte and acid–base disorders was significantly higher in hypokalemic compared to normokalemic patients. Additionally, patients with marked hypokalemia

(serum K^+ < 2.8 mmol/l) exhibited a higher incidence of hypophosphatemia, hypomagnesemia, and acid–base derangements compared to patients with mild hypokalemia (serum K^+ 2.8–3.3 mmol/l) [Table IIIB]. Interestingly, in hypokalemic patients serum K^+ levels were well correlated with serum Mg^{2+} ($R = 0.34$, $P < 0.01$) and PO_4^{3-} ($R = 0.31$, $P < 0.05$) levels. Furthermore, the state of the disease does not seem to significantly influence the presence of these abnormalities, which were equally evident in patients at disease remission, after relapse, or on first diagnosis (data not shown).

DISCUSSION

Alterations of the water-electrolyte balance are not infrequent disease-associated complications in patients with acute leukemia. Although not life-threatening per se, these abnormalities may be hazardous because of the potential chemotherapy-related cardiotoxic effects. In fact, fatal complications, such as sudden death due to malignant arrhythmias, have been reported in leukemic patients as an associated synergistic effect between anti-neoplastic drugs and electrolyte disorders [2,18,19]. However, considering the need for prompt initiation of treatment in patients with acute leukemia, clinicians should be vigilant for early detection and correction of concurrent acid–base and electrolyte disturbances along with the treatment of the disease. It is of interest that in our study electrolyte and acid–base abnormalities may be present regardless of the blast cell type (AML or ALL) or the state of the disease. It must be considered, however, that disease- or chemotherapy-associated complications may significantly contribute to the pathogenesis of these disturbances. In the following section, we focus on the responsible interrelated pathophysiological mechanisms for the acid–base and electrolyte abnormalities in the studied population.

In our study, hypokalemia was the most pronounced electrolyte abnormality. Hypokalemia, although noted, remains a poorly illuminated complication in leukemic patients, primarily in patients with acute monocytic and acute myelomonocytic leukemia (M4 and M5), and has been mainly attributed to lysozymuria-induced renal tubular injury with kaliuresis [3,20–23]. In our cohort, the majority of hypokalemic patients had either M4 or M5 AML, but hypokalemia was also found in the other histological types. Even though the association between lysozymuria and renal K^+ wasting is well documented, hypokalemia and inappropriate kaliuresis could be due to other mechanisms as well. In our study, serum K^+ levels were inversely correlated with FE K^+ , suggesting the important role of kaliuresis in producing K^+ depletion in leukemic patients. Abnormal urinalysis findings (including granular casts) in some hypokalemic patients is also indicative of a probable association between renal K^+

depletion and tubular dysfunction beyond lysozymuria (24). Moreover, it is well established that hypomagnesemia of any cause produces K^+ depletion due to both urinary and fecal losses [25,26]. In fact, serum K^+ levels were well correlated with serum Mg^{2+} levels, while hypomagnesemia was noted concurrently with kaliuresis in 18 patients. Finally, despite the absence of correlation between hypokalemia and arterial pH as well as white blood cell count, it should be pointed out that K^+ entry into metabolically active cells may also contribute to serum K^+ levels decrease [27], as it was noticed in patients with alkalemia (9 patients) and marked leukocytosis (6 patients).

Hyponatremia was infrequently noticed in our patients (6 cases). Hypovolemic hyponatremia (volume contraction due mainly to gastrointestinal fluid losses) was noted in 4 patients. One patient fulfilled the criteria of SIADH (syndrome of inappropriate ADH secretion) [16]. Even though neoplasias are among the commonest causes of SIADH [28,29], hyponatremia and hypochloremia secondary to SIADH have been infrequently reported in the setting of acute leukemia, and they are related either to the leukemic process per se [2] or to high-dose cytosine arabinoside chemotherapy, which was not the case in our patient [30]. Additionally, no hyponatremic patient had any evidence of underlying infection or CNS involvement, which are common causes of SIADH in the everyday clinical practice. Finally, salt-losing nephropathy was diagnosed to be the cause of hyponatremia in one patient with evidence of mild renal function decline, abnormal urinalysis findings, and hypovolemia. The patient had no history of underlying renal disease or analgesic abuse, thus implicating a leukemia-induced tubular defect as the cause of renal Na^+ wasting.

Hypomagnesemia was evident in about one third of leukemic patients. According to our data no correlation was exhibited between serum Mg^{2+} levels and total leukocyte count or arterial pH, though increased transcellular Mg^{2+} shift from the extracellular to intracellular space may have contributed to the decreased serum Mg^{2+} levels, especially in patients with marked leukocytosis as well as in the three patients with alkalemia [31,32]. Additionally, increased gastrointestinal Mg^{2+} loss is probably the main pathogenetic mechanism of hypomagnesemia in patients with acute or chronic diarrhea. However, hypomagnesemia coexisting with inappropriate magnesuria was noticed in eight patients, suggesting that increased Mg^{2+} urinary losses may play a role in the pathogenesis of Mg^{2+} depletion. Inappropriate magnesuria could be due to leukemia-induced and/or lysozyme-induced tubular dysfunction. It is well known that in patients with acute leukemia renal impairment may be associated either with glomerular or tubular dysfunction [2,20,23]. Indeed, in our study, active urinary sediment was associated with magnesuria (in 5 patients). More-

over, it has been shown that leukemic cell products other than lysozyme are also linked to renal tubular injury and increased electrolyte excretion [20]. Finally, metabolic acidosis and phosphate depletion observed in some hypomagnesemic patients could have been responsible for the inappropriate magnesuria, which has been shown to arise from reduced Mg^{2+} reabsorption in the loop of Henle as well as in the distal tubule [33,34].

In some patients no apparent cause for hypomagnesemia was found. This pronounced fall in serum Mg^{2+} levels in these patients might be due to a low Mg^{2+} intake owing to malnutrition commonly encountered in patients with acute leukemia.

Hypophosphatemia, described in acute leukemia patients, has been occasionally ascribed to a decreased PO_4^{3-} intake, but the leading causes are either a shift of PO_4^{3-} ions into rapidly growing tumor cells or inappropriate urinary loss [35–37]. In our study, serum PO_4^{3-} levels were inversely correlated with $FEPO_4^{3-}$, signifying the importance of phosphaturia in producing PO_4^{3-} depletion. Hypophosphatemia and associated inappropriate phosphaturia was observed in 5 patients with concurrent hypomagnesemia and in 2 patients with acidemia. Even though hypophosphatemia could be the cause of inappropriate magnesuria and hypomagnesemia, in some cases it might also be the result of hypomagnesemia, since in experimental Mg^{2+} depletion phosphaturia unrelated to parathyroid hormone activity is a common finding and is suggested to be due to a proximal defect in PO_4^{3-} transport [38,39]. Acute metabolic acidosis causes loss of PO_4^{3-} in the urine and enhances cellular release of the PO_4^{3-} anions [40]. In cases of unexplained phosphaturia, tubular dysfunction (indicated by urinary casts and phosphate crystals) may be implicated. Young et al. recently described a case of severe hypophosphatemia due to both increased utilization of PO_4^{3-} by rapidly growing tumor cells, as well as tubular defect-associated excessive PO_4^{3-} urinary loss [36]. The authors suggested that in the presence of severe hypophosphatemia, intracellular PO_4^{3-} depletion might occur in renal tubular cells, potentially interfering with urinary PO_4^{3-} reabsorption. Intracellular shift of PO_4^{3-} is probably the cause of hypophosphatemia in patients with high white cell counts and alkalosis, even though no correlation was exhibited between PO_4^{3-} levels and white cell count or pH [41].

Hypocalcemia has been occasionally reported in patients with acute leukemia [42] and is mainly ascribed to hypoalbuminemia. However, the most common cause of hypocalcemia is the coexistent hypomagnesemia, which impairs the release of parathyroid hormone (PTH) and induces skeletal resistance to PTH [43,44]. Furthermore, chronic respiratory alkalosis may have played a prominent role in the development of hypocalcemia in some patients, since it has been reported to be associated with renal PTH-resistance and hypercalciuria [45]. In 3 pa-

tients multifactorial origin hypocalcemia could be the result of bacteremia [46,47]. Calciuria could have contributed to hypocalcemia in a considerable number of patients. In such cases, it could be due to a primary tubular lesion (evidenced by the active urinary sediment) or to hypophosphatemia, which stimulates the production of 1,25-dihydroxy-vitamin D leading to an augmented intestinal Ca^{2+} absorption with a resulting hypercalciuria [48,49].

Beyond the simple acid–base disturbances observed (respiratory alkalosis and metabolic alkalosis) whose etiology is profound (hypoxemia and increased upper gastrointestinal losses in concert with hypovolemia and hypokalemia), a number of mixed acid–base disorders were found in our cohort. Special attention should be drawn to the correct and careful interpretation of acid–base and electrolyte parameters in order to disclose and elucidate the underlying mechanisms of these mixed acid–base disorders. Underlying infection may have played a prominent role in the development of these derangements. For example, in 4 patients septicemia was associated with a combination of respiratory alkalosis (due to hyperventilation) and metabolic acidosis (possibly due to lactic acidosis). Additionally, in two patients with an acute diarrheal illness a combination of diarrhea-induced hyperchloremic metabolic acidosis and respiratory alkalosis was evident. Finally, in two patients with severe lower respiratory infection and hypoxemia, a combination of respiratory acidosis and metabolic alkalosis was found. It is noteworthy that acid–base disorders were noticed not only in patients with AML but in ALL patients as well. However, our limited data in ALL patients (low incidence in adults) obviate speculations on possible statistical differences.

Remarkably in our study, acid–base and electrolyte disturbances were more commonly observed in K^+ depleted patients, while the severity of hypokalemia was well correlated with both the incidence and the severity of these abnormalities. Thus, for the first time in the literature in patients with acute leukemia hypokalemia is reported to be an important diagnostic tool towards the disclosure of multiple concurrent, interrelated electrolyte and acid–base disorders, especially in patients with acute myeloid leukemia. Moreover, acid–base and electrolyte abnormalities are described in both AML and ALL patients, indicating underlying common pathogenetic mechanisms leading to renal tubular dysfunction.

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