Life threatening hypophosphataemia in a patient with Philadelphia chromosome-positive chronic myelogenous leukaemia in acute blastic crisis

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Summary: Life-threatening hypophosphataemia developed in a 47 year old woman with blastic crisis of chronic myelogenous leukaemia. The patient's hospitalization was characterized by reciprocal relationship between her white cell count and the serum phosphorus levels. The patient did not demonstrate any of the usual causes of profound hypophosphataemia. The postulated mechanism of this patient's hypophosphataemia is uptake by the rapidly dividing leukaemic cells. To the best of our knowledge this is the first case in the English literature of hypophosphataemia associated with blast crisis of Philadelphia chromosome-positive chronic myelogenous leukaemia.

Introduction

Several conditions are known to induce moderate to severe hypophosphataemia. Although it is well established that rapid cell synthesis and turnover may be associated with high phosphorus consumption, hypophosphataemia is a relatively infrequent complication of neoplastic diseases and, if at all, is usually associated with parathyroid hormone-like peptide production.¹ Hypophosphataemia associated with haematological malignancies has been reported infrequently.^{1–14}

We report here a patient with Philadelphia chromosome-positive chronic myelogenous leukaemia (CML) in acute blastic crisis who had episodes of profound symptomatic hypophosphataemia preceding the rise in number of peripheral blasts. The apparent cause for this patient's hypophosphataemia was uptake by the leukaemic blasts.

To the best of our knowledge this is the first case in the English literature of hypophosphataemia associated with blast crisis of Philadelphia chromosome-positive CML.

Case report

A 47 year old woman, suffering from Philadelphia chromosome-positive CML, was admitted to the

hospital because of pain in both hip joints and fever. There was a history of non-insulin-dependent diabetes mellitus.

Physical examination revealed an ill and pale patient. Temperature was 38°C, pulse 120 beats/min and regular. There was generalized lymphadenopathy. A firm tender spleen and liver were palpable. Haemoglobin level was 8.7 g/dl, white cell count (WBC) was $80.5 \times 10^9/l$ on admission and rose to $197.0 \times 10^9/l$ within the next 3 days, with 30% blast forms. Platelets were $29 \times 10^9/l$. A diagnosis of acute blast crisis, myelomonocytic type, based on cytochemical and immunological evaluation was established.

Serum sodium was 136 mmol/l, potassium 4.2 mmol/l, uric acid 375 $\mu\text{mol/l}$, calcium 2.2 mmol/l and phosphorus 1.19 mmol/l. Serum urea nitrogen and the creatinine which were 6.86 mmol/l and 202 $\mu\text{mol/l}$, respectively, decreased to normal values after hydration. Blood glucose levels were within normal limits. The remainder of the laboratory tests were within normal limits. The patient was treated with daunorubicin 30 mg/m² and increase of the hydroxyurea dosage to 3.0 g daily.

During the following weeks a consistent relationship between the WBC and the serum phosphorus concentrations was noted. There were 5 cycles of hypophosphataemia. Each cycle was characterized by a precipitous fall in the phosphorus concentration to extremely low levels, preceding a rapid rise in the WBC to extremely high values. After each increase in WBC, daunorubicin was administered with subsequent decrease in WBC and increase in

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phosphorus levels (Figure 1).

The extreme hypophosphataemia in the patient was accompanied by symptomatic heart failure and neurological symptoms including tachycardia, dyspnoea, peripheral oedema and perimetal paresthesias.

Although an extensive search for an infectious agent failed to reveal a pathogen, the patient was treated with broad spectrum antibiotics including amphotericin B. Nevertheless, despite all efforts, the patient died on her 76th hospitalization day. Permission for autopsy was not granted.

Special studies

In evaluation of the aetiology of the patient's hypophosphataemia the following studies were performed. Parathyroid hormone values were measured twice at between 50 and 60 pmol/l (normal values 30–85 pmol/l, midmolecule parathyroid hormone RIA). 1,25-dihydroxyvitamin D (radioceptor assay) was 37.1 picograms/ml (normal values: 16–42 pg/ml). Urinary cAMP measured 3 mmol/l (normal values 2–4 mmol/ml) and tubular reabsorption of phosphate (TRP) ranged from 98.7–98.8% during periods of profound hypophosphataemia (normal values >85%).

Discussion

Several potential causes that could contribute to our patient's hypophosphataemia were ruled out, namely nutritional causes, antacids ingestion, renal phosphorus loss, sepsis or diabetic ketoacidosis.^{3,15–17}

Figure 1 Phosphorus levels and white cell counts changes during patient's hospitalization. The solid line represents the white cell counts and the broken line the phosphorus levels. H represents increase in the hydroxy-urea dosage. D represents daunorubicin administration.

Acute leukaemia by itself is capable of altering the normal physiological regulation of most electrolytes.^{1,2,4,5,11–14} Table I lists the reported cases of leukaemia-associated hypophosphataemia.

In this patient there was no evidence that the cause of hypophosphataemia was hyperparathyroidism, osteoblast stimulating factor production, interference with 25-hydroxylation of vitamin D₃, renal tubular leak due to lysosymuria or oncogene osteomalacia.^{1,3–5,15,18–24}

Severe hypophosphataemia has occasionally been reported in coincidence with blast cell proliferation in haematological patients (Table I).^{1,3,6–10} Hypophosphataemia in those cases was usually attributed to the excessive uptake of phosphorus by the proliferating cells. In these patients, as in our patient, TRP, if measured, was very high during periods of blastic replication and decreased after the initiation of chemotherapy with cell lysis and the development of hyperphosphataemia.

The data in the present case suggest that the decrease in phosphate levels was due to changes in its transcellular distribution. The rapid replication of the malignant cells might have increased the demand for phosphate by its uptake by the rapidly dividing cells, resulting in profound hypophosphataemia. The high TRP values during periods of severe hypophosphataemia and the fact that the rapid fall in serum phosphate concentrations had begun several days *before* the steep rise in peripheral blast counts, strongly suggest transcellular shift with intracellular trapping of phosphorus in the replicating cells, as the possible mechanisms for hypophosphataemia in this patient. A postulated mechanism for this hypothesis is based on the fact that blast cells derived from the myeloid series fail to show inhibition of glycolysis by oxygen.³ Therefore, in the presence of ambient concentrations of oxygen, myeloblasts show increased rates of aerobic glycolysis as compared to normal myeloid tissue. The enhanced rate of aerobic glycolysis that the leukemic myeloblasts undergo causes redistribution of large amounts of extracellular phosphate into the intracellular environment to provide phosphate for glycolytic intermediates.¹⁷ This causes a fall in phosphate levels in the blood and in non-myeloid tissues, with hypophosphataemia ensuing despite total body phosphorus in the normal range.

In Figure 1, one can see a lag of 4–5 days between the beginning of the decline in serum phosphorus levels and that of the steep rise in the number of blasts in peripheral blood. This can be explained by the fact that there is a transit time of 2–5 days between blast cells genesis in bone marrow and their appearance in peripheral blood. During this period, the leukaemic blasts in the bone marrow use phosphate for their enhanced metabolic activity, including the aerobic glycolysis. This might lead to a fall in serum phosphate levels before

Table I Leukaemia-associated hypophosphataemia

Leukaemia type	Serum levels		Urine P levels	Symptoms and signs	Postulated mechanism	Reference
	Ca (mmol/l)	P (nmol/l)				
Acute myelomonocytic Lymphoblastic	High 2.4	Low 0.095	– Very low	Bone pain Lethargy, blurred vision, muscle weakness, thrombocytopenia Neuromuscular	Parathyroid-hormone-like Antacids, steroids	4 11
Acute myelogenous	1.8	0.19	–	Congestive heart failure Liver dysfunction	Starvation, gentamicin, i.v. glucose, sepsis, acetazolamide	2
Chronic lymphatic Myeloma, chronic lymphocytic	High –	Low Low	Low High	– Fanconi syndrome	Hyperparathyroidism Oncogenous osteomalacia; light chain nephropathy and renal tubular dysfunction	12 13
Acute myeloblastic	High	Low	–	–	Ectopic parathyroid hormone like-leukaemic origin	14
Acute myelomonocytic	1.6	0.88	–	Tetany, congestive heart failure; torsade de pointes	Osteoblastic stimulating factor, accelerated bone formation	5
Hairy cell	2.0	0.57	–	–	Increased transcellular uptake	8
Acute myelomonocytic	1.3	0.063	Undetected	Acute respiratory failure	Increased transcellular uptake	3
Lymphoma blastic crisis	–	0.15	Undetected	–	Increased transcellular uptake	9
Burkitt's lymphoma leukaemia	–	Low	–	Facial nerve palsy, muscle weakness, arthralgia	Increased transcellular uptake	10
Chronic myelocytic leukaemia-blastic crisis	Normal	0.063	Very low	Respiratory failure	Increased transcellular uptake	6
Acute lymphoblastic	2.25	0.28	Low	–	Increased transcellular uptake	7
Histiocytic lymphoma leukaemic phase	1.95	0.22	Undetected	–	Increased transcellular uptake	1

Ca = calcium; P = phosphorus.

the overt appearance of leukaemic blasts in peripheral blood.

There is a possibility therefore, that in patients with blastic crisis, hypophosphataemia should be considered as an index of enhanced disease activity even before there is evidence for it in the peripheral blood smear. Serum phosphate concentration

should therefore be closely monitored in such patients and bone marrow aspiration and treatment should be considered in a leukaemic patient presenting with severe hypophosphataemia, even before an increase in white cell count in peripheral blood is noticed.

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