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Brief report

Hyperphosphatemia in tumor lysis syndrome: the role of hemodialysis and continuous veno-venous hemofiltration

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Abstract. We report a 4-year-old boy who developed tumor lysis syndrome complicated by severe hyperphosphatemia and acute renal failure, following chemotherapy for T-cell acute lymphoblastic leukemia. Despite successful treatment of hyperphosphatemia with hemodialysis, there was an immediate rebound in the high serum phosphorus level. The patient underwent a second treatment with hemodialysis which was then followed by continuous veno-venous hemofiltration (CVVH). CVVH maintained his serum phosphorus at a stable level until his renal function improved. CVVH can be used in conjunction with hemodialysis to successfully treat the hyperphosphatemia associated with tumor lysis syndrome.

Key words: Tumor lysis syndrome – Hyperphosphatemia – Hemodialysis – Continuous veno-venous hemofiltration – Acute renal failure

Introduction

Tumor lysis syndrome is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which occur as a result of neoplastic cell lysis due to either chemotherapy or high cell turnover in acute leukemia and malignant lymphoma [1,2]. There is a high incidence of renal failure in this syndrome, as a result of uric acid nephropathy [1]. Hyperphosphatemia, by precipitation of phosphorus with calcium in the renal tubules, has also been implicated as a cause of acute renal failure and has been the focus of several reports [3, 4]. Hemodialysis is recommended for the treatment of acute hyperphosphatemia, however little is known about its efficacy in phosphate removal [5]. The purpose of this report is to describe the use of hemodialysis and continuous veno-venous hemofiltration (CVVH) to treat hyperphosphatemia in a patient who developed tumor lysis syndrome resulting from T-cell acute lymphoblastic leukemia (ALL).

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Case report

A 4-year-old Hispanic male was admitted to Children's Medical Center of Dallas with a diagnosis of T-cell ALL. On admission his laboratory values included: a white blood cell (WBC) count of 61,900/mm^3 with 59% lymphoblasts, hemoglobin 11.5 g/dl, platelets 143,000 per mm^3, uric acid 10.0 mg/dl, serum creatinine 0.5 mg/dl, blood urea nitrogen (BUN) 8 mg/dl, calcium 10.0 mg/dl, and phosphorus 4.1 mg/dl. The bone marrow was replaced with lymphoblasts which reacted with monoclonal antibodies directed against T-cell-specific antigens.

Before chemotherapy, the patient was treated with a standard protocol for intravenous hydration (3,000 ml/m^2 per 24 h), alkalinization of the urine, and allopurinol (15 mg/kg per 24 h in 3 8-hourly divided doses). Induction chemotherapy was planned according to Pediatric Oncology Group Protocol no. 9297, which consisted of systemic prednisone, vincristine, cyclophosphamide, and doxorubicin, and intrathecal methotrexate, hydrocortisone, and cytarabine. He was initially given prednisone alone (40 mg/m^2 per 24 h) and within 48 h his WBC count had decreased to 2,300/mm^3.

He developed oliguric acute renal failure within 48 h of initiating prednisone, with his serum creatinine increasing to 1.3 mg/dl and BUN to 33 mg/dl. His serum phosphorus increased to 19.1 mg/dl (Fig. 1) and his calcium decreased to 4.5 mg/dl. Hemodialysis was initiated with a Toray B 2.1 dialyzer and blood flow between 200 and 225 ml/min to treat the severe hyperphosphatemia, and after 4 h his serum phosphorus was reduced to 6.7 mg/dl. A second hemodialysis treatment was initiated within 4 h of stopping the first treatment because the serum phosphorus had increased to 19.3 mg/dl. At the end of the second treatment he was immediately placed on CVVH (bm 11 Blood Monitor Pump, Baxter, Ill., USA) using a diafilter 20 cartridge (Amicon, Danvers, Mass., USA) with a blood flow of 200 ml/min and an ultrafiltration rate of 800 ml/h. Predilution fluid was given at a rate to ensure the patient remained euvolemic. When CVVH was initiated his serum phosphorus was 6.2 mg/dl. It never exceeded

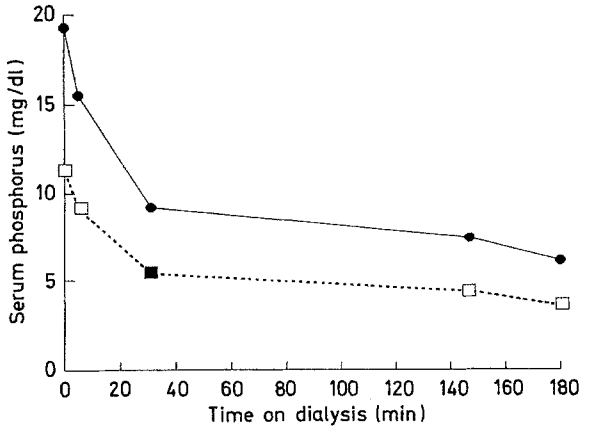

Fig. 1. Time course of serum phosphorus levels during the second hemodialysis treatment. *Closed circles* represent measured values of predialyzer phosphorus and the *closed square* represents the measured postdialyzer phosphorus level. The *open squares* represent predicted levels of postdialyzer phosphorus assuming a constant extraction ratio. The amount of phosphorus removed during the hemodialysis treatment can be calculated as the area between the two curves multiplied by the blood flow rate

8.8 mg/dl during the 52 h of CVVH and was 5.4 mg/dl when CVVH was terminated due to return of normal renal function. During the rest of his hospitalization, his serum phosphorus never exceeded 6.1 mg/dl.

During the second hemodialysis treatment, the clearance of phosphorus was determined by measuring a pre- and postdialyzer phosphorus level, and was found to be 92 ml/min. Urea clearance at the same time was 166 ml/min. The serum phosphorus level was also monitored during the treatment so that the total amount of phosphorus removed could be determined. This was found to be 1,670 mg for the 3-h treatment, giving an average of 9.3 mg/min. While on CVVH, the ultrafiltrate phosphorus concentration was 7.8 mg/dl, which gives a phosphorus removal rate of 1.0 mg/min or 1,440 mg/24 h.

Discussion

Hyperphosphatemia is a frequent complication of tumor lysis syndrome [1, 2]. In one series, hyperphosphatemia developed in 10 of 32 nonazotemic patients and in all 14 azotemic patients [1]. Hyperphosphatemia has also been implicated as a cause of acute renal failure in tumor lysis syndrome, by the precipitation of phosphorus with calcium in the renal tubules [3, 4]. The phosphorus load comes from the destruction of lymphoblasts, which have four times the amount of organic and inorganic phosphorus as mature lymphocytes [6]. In parallel with the significant drop in the patient's WBC count from 61,900/mm^3 to 2,300/mm^3 following administration of prednisone, his serum phosphorus increased to 19.1 mg/dl. The patient's uric acid level was concomitantly declining, despite the development of renal failure. Serum and urine levels of xanthine were not measured, so the possibility of acute xanthine nephropathy cannot be excluded [7].

Hemodialysis is the recommended treatment for severe hyperphosphatemia, however little is known about the efficacy of hemodialysis for phosphorus removal. A recent study in adults indicates that during a 4-hour conventional hemodialysis treatment only 511 ± 222 mg of phosphorus can be removed [8]. Hemodialysis removes phosphorus by diffusion, so the rate of removal is directly proportional to the serum concentration. Phosphorus removal in the present patient was 1,670 mg for the 3-hour treatment, which averaged 9.3 mg/min. However, the initial rate of phosphorus removal, when the serum concentration was 19.3 mg/dl, was 17.8 mg/min. The removal rate at the end of the treatment, when the serum concentration was 6.2 mg/dl, was only 5.7 mg/min.

CVVH removes phosphorus by convection and is therefore proportional to the serum concentration and the ultrafiltration rate. At the time when CVVH was initiated, the patient's serum phosphorus concentration was 6.2 mg/dl, which gave a removal rate of 0.7 mg/min when the ultrafiltration rate was 800 ml/h (13.3 ml/min). If the serum phosphorus concentration was 19.3 mg/dl, the phosphorus removal rate would have been 2.3 mg/min. While these removal rates are well below those for hemodialysis, the rate was sufficient to prevent an increase in his serum phosphorus and prevented the need for subsequent treatment with hemodialysis.

Hyperphosphatemia in this patient was caused by the release of phosphorus from lymphoblasts after the initiation of prednisone [6]. The rate of production of inorganic phosphorus would have been steadily declining as the WBC count was decreasing and could also explain why the serum phosphorus concentration remained stable while on CVVH. If the rate of phosphorus production after the first hemodialysis treatment was comparable to the rate of phosphorus removal with CVVH, the second hemodialysis treatment may have been avoided if the patient had been placed on CVVH immediately after the first dialysis treatment.

Hyperphosphatemia is a common complication of tumor lysis syndrome. The treatment of severe hyperphosphatemia in acute renal failure is hemodialysis. In cases where there is ongoing accumulation of phosphorus, repeated treatments with hemodialysis may be indicated. This patient demonstrates the efficacy of CVVH in maintaining a stable serum phosphorus concentration after hemodialysis has been used to treat the hyperphosphatemia.

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Literature abstracts

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Levels of growth hormone, insulin-like growth factor-I (IGF-I) and -II, IGF-binding protein-1 and -3, and cortisol in prednisone-treated children with growth retardation after renal transplantation

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Growth retardation after renal transplantation (RTx) is generally attributed to prednisone (PDN) administration, although the exact mechanism is poorly understood. In a group of 19 growth-retarded post-RTx children, we studied the effect of alternate day (AD; $n = 12$) and daily (D; $n = 7$) PDN therapy (0.10–0.25 mg/kg·day) on 24-h plasma GH and cortisol profiles, once in group D and twice on successive days in group AD. The maximal plasma GH response to arginine provocation (ATT) and plasma levels of insulin-like growth factor-I (IGF-I), IGF-II, and serum IGF-binding proteins (IGFBP) were also determined.

The pulsatile character of the 24-h GH secretion was sustained in all patients. However, mean GH levels were significantly lower as compared with published data for healthy children, corrected for pubertal stage and sex. The highest mean GH levels were found in boys and girls in late puberty. Group AD had similar 24-h GH profiles whether on or off PDN treatment, which did not differ significantly from the GH profiles observed in group D. The maximal GH response during ATT was greater than 10 μg/l in 57% of the children. Group D had significantly lower mean and maximal cortisol levels than group AD, but all patients had a normal diurnal variation. Plasma immunoreactive IGF-I and IGF-II, and serum IGFBP-1 levels were normal, but serum levels of IGFBP-3 were increased. A significant negative correlation was found between the glomerular filtration rate and serum IGFBP-3 levels.

In conclusion, our findings indicate that growth-retarded renal allograft patients, receiving either alternate day or daily PDN therapy, have decreased GH secretion, but a normal diurnal rhythm of GH and cortisol secretion as well as normal plasma IGF-I and -II levels. However, growth retardation after RTx may not solely be the result of decreased GH secretion. Renal graft impairment together with decreased IGF bioavailability may, in addition to the presumed direct effects of PDN on cartilage, contribute to the growth retardation after RTx.

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Renal function in neonatal hyperbilirubinemia

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A total of 75 jaundiced infants with gestational ages ranging from 37 to 42 weeks were studied during the first 10 days of age to evaluate renal function by measuring endogenous creatinine clearance (Ccr), fractional excretion of N-acetyl-β-*D*-glucosaminidase (NAG) to creatinine, fractional excretion of sodium (FENa) and urine osmolality. All jaundiced infants were divided into two groups. Group 1 infants ($n = 35$) had total serum bilirubin levels ranging between 21 and 39.6 mg/dl (mean 27.2). Exchange transfusions were performed in all group 1 infants at the time of the initial study. Group 2 infants ($n = 40$), whose total serum bilirubin levels ranged between 12.3 and 20 mg/dl (mean 16.4), received phototherapy, except for 2. Conjugated bilirubin levels were less than 1.0 mg/dl in all these infants. Results were compared with 25 untreated control infants with corresponding gestational and postnatal ages. Follow-up studies were done in 27 of the 35 group 1 infants and in 32 of the 40 group 2 infants prior to hospital discharge, when total serum bilirubin levels had decreased to less than 10 mg/dl. Ccr, fractional excretion of NAG to creatinine, FENa and urine osmolality of group 1 infants were statistically significantly different when compared to those of group 2 and the control infants. The measured parameters in the post-treatment follow-up study of group 1 infants returned to near-normal levels when total serum bilirubin levels became normal. However, no significant differences were seen between group 2 and the control infants in any of the measured parameters. It is concluded that unconjugated bilirubin is directly involved in the impairment of glomerular filtration and tubular functions in infants with high levels of serum unconjugated bilirubin (> 20 mg/dl). Renal function defects are transient and reversible and can be prevented by lowering serum bilirubin levels to near-normal levels.