

Clinical and Laboratory Observations

Severe Hyperphosphatemia Resulting From High-Dose Liposomal Amphotericin in a Child With Leukemia

Anita Jain, M.D., and Lavjay Butani, M.D.

Summary: Children with acute lymphoblastic leukemia (ALL) are at risk for serious electrolyte abnormalities. The authors report their experience in managing a child with ALL who developed severe hyperphosphatemia as a consequence of a large exogenous load of phosphorus from high-dose liposomal amphotericin B. Health care providers need to recognize this potentially life-threatening complication of liposomal amphotericin B, since early detection and intervention can prevent significant morbidity.
Key Words: Amphotericin B—Electrolyte abnormalities—Hyperphosphatemia—Liposomal.

Hyperphosphatemia can occur as a consequence of a variety of different disease processes (1). In children, the most common cause of hyperphosphatemia is decreased renal phosphate excretion, either from renal insufficiency or as a result of hypo- or pseudohypoparathyroidism. Other causes of hyperphosphatemia include vitamin D intoxication, internal redistribution by acute metabolic and respiratory acidosis, rhabdomyolysis, hemolytic processes, and as a part of the tumor lysis syndrome in patients during induction chemotherapy for leukemia and lymphoma (2).

Severe hyperphosphatemia is a potentially life-threatening condition, since it can lead to ectopic calcification in vessel walls. The extensive degree of calcific deposits has been noted to result in tissue ischemia, acute respiratory failure, and even cardiac arrhythmias (3). These risks are greatly increased when the calcium-phosphorous product exceeds 70 (2). We are reporting our experience in caring for an 8-year-old child with acute lymphoblastic leukemia (ALL) who developed severe hyperphosphatemia while receiving high-dose intravenous (IV) liposomal amphotericin B (AmBisome, Fujisawa Healthcare Inc., Deerfield, IL, U.S.A.) for a frontal lobe fungal abscess. This promptly resolved after stopping the medication. This previously unreported complication of IV AmBisome put the patient at risk for developing life-threatening consequences.

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From the Department of Pediatrics, University of California, Davis, Davis, California, U.S.A.

Address correspondence and reprint requests to Lavjay Butani, M.D., Section of Pediatric Nephrology, Department of Pediatrics, University of California, Davis, Medical Center, Ticon II Building, 3rd Floor, 2516 Stockton Boulevard, Sacramento, CA 95817, U.S.A. E-mail: Lavjay.butani@ucdmc.ucdavis.edu

CASE REPORT

An 8-year-old girl undergoing reinduction therapy for relapsed ALL, originally diagnosed 3 years previously, was admitted with new-onset seizures, severe intermittent headaches, and right-sided eye pain. An MRI of the head and sinuses revealed acute pansinusitis and orbital cellulitis with lateral displacement of the medial rectus muscle of the right eye; a large soft tissue mass was also seen in the right frontal lobe. The patient's admission serum chemistries were significant for a normal serum creatinine (0.3 mg/dL), a low serum phosphorus of 2.4 (normal 3.4–5.9) mg/dL, a normal serum potassium of 3.5 mEq/L, and a normal serum bicarbonate of 24 mEq/L. Her serum uric acid and lactate dehydrogenase (LDH) levels were both normal.

The patient underwent maxillary sinus surgical debridement; on tissue culture *Mucormycosis*, *Aspergillus*, and *Candida albicans* were isolated. IV AmBisome was started at conventional doses of 5 mg/kg per day. Since a second MRI a week later showed progression of the frontal lobe abscess, the AmBisome dose was increased to 25 mg/kg per day. Although experience with such high a dose of AmBisome has not been previously reported, this dose escalation was performed upon the recommendations of the pediatric infectious disease specialist who was closely involved in the care of the patient.

For the duration of her hospital stay the patient remained afebrile and seizure-free. A bone marrow aspirate and lumbar puncture revealed that her ALL was in remission. Serum chemistries, excluding a serum phosphorus, were obtained on a daily basis during this time and were completely normal. After 7 days of high-dose IV AmBisome, a comprehensive metabolic panel, which included serum phosphorus, was obtained and revealed a markedly elevated phosphorus level of 16.8 mg/dL, with a normal serum calcium level of 8.9 mg/dL. A repeat metabolic panel the next day confirmed the elevated serum phosphorus level (19.0 mg/dL). All the

other serum chemistries at this time were normal; the serum creatinine was 0.4 mg/dL, the serum potassium was 3.7 mEq/L, and the serum bicarbonate was 23 mEq/L.

Serum parathyroid hormone (PTH), vitamin D, and urinary creatinine and phosphorus levels were obtained. Suspecting that the patient's hyperphosphatemia was related to high-dose IV AmBisome use, and because she was clinically improved, the AmBisome was discontinued and replaced with oral itraconazole. She was also started on oral calcium carbonate (as a phosphate binder) to prevent gastrointestinal absorption of phosphorus from her diet. The patient never became oligoanuric, nor was she receiving oral vitamin D supplementation.

Subsequent laboratory tests showed an elevated PTH of 106 (normal 10–65) pg/mL with suppressed 1,25-vitamin D and 25-vitamin D levels of 6 (normal 15–75) pg/mL and 13 (normal 15–57) pg/mL, respectively. The patient's urinary indices showed a low tubular resorption of phosphorous (TRP) at 78% (normal >85%). Three days after discontinuation of IV AmBisome, the patient's serum phosphorus level had decreased to 8.1 mg/dL, and by 2 weeks it had normalized to 3.6 mg/dL (Fig. 1).

Because the patient was doing well clinically, the family elected not to pursue surgical intervention for the brain abscess. At last follow-up, 18 months after the diagnosis of *Mucormycosis*, the patient is alive and neurologically stable. Her most recent MRI has shown complete resolution of the brain abscess.

DISCUSSION

Electrolyte disturbances frequently occur in children with acute leukemia. Abnormalities such as hyponatremia, hypo- and hyperkalemia, and hypo- and hyperphosphatemia may be encountered. Tumor cell lysis, either spontaneously from a high tumor burden or following initiation of chemotherapy, can lead to hyperphosphatemia as part of the so-called tumor lysis syndrome (4). Our patient had no clinical or laboratory evidence of tumor lysis, in that her bone marrow showed the ALL to be in remission, and her serum uric acid and LDH were both normal. Her laboratory values showing an elevated PTH, suppressed vitamin D, and low TRP (2) all pointed toward an exogenous source of phosphorus as the cause of her hyperphosphatemia, with an appropriate renal and parathyroid compensatory response.

Amphotericin B acts by binding to the sterol component of fungal cell membranes, leading to alterations in cell permeability and cell death. AmBisome is a sterile, nonpyrogenic lyophilized product for IV infusion. Each vial contains 50 mg amphotericin B, USP, intercalated into a liposome membrane consisting of, among other compounds, approximately 213 mg hydrogenated soy phosphatidylcholine and 84 mg distearoylphosphatidylglycerol, giving a net inorganic phosphorus concentration of 37 mg per vial of AmBisome. Since our patient was receiving a daily AmBisome dose of 500 mg (25 mg/kg per day), her exogenous nondietary phosphorus load amounted to approximately 370 mg (≈20 mg/kg per day), which is clearly in excess of what can be safely handled by the kidney, especially in a patient who, having previously received nephrotoxic chemotherapeutic agents, probably had marginal renal reserve to begin with.

Our patient's serum phosphorous level rapidly increased after starting IV AmBisome to a life-threatening 19 mg/dL and then, just as rapidly, normalized after discontinuation of the medication (see Fig. 1). This reaffirmed our suspicion that the hyperphosphatemia was a direct consequence of the high phosphorus content of the AmBisome preparation.

The purpose of our report is to make health care professionals aware of this previously unreported and life-threatening complication of high-dose IV AmBisome, espe-

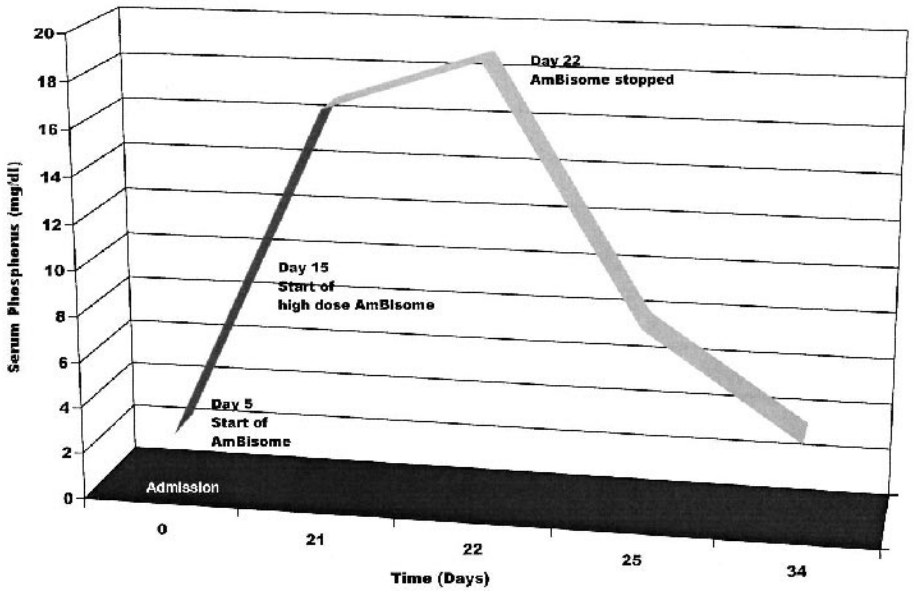

FIG. 1. Temporal relation between serum phosphorus levels and AmBisome therapy.

cially since the use of AmBisome has increased due to the more prolonged neutropenic states encountered since the introduction of intense chemotherapy for aggressive leukemias. Therefore, we are advocating that patients started on IV AmBisome have serum chemistries (including serum phosphorus) monitored on a routine basis to allow for early detection of hyperphosphatemia so that the medication dose can be adjusted promptly to prevent serious complications.

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