Chapter 60

Oncologic Emergencies: Tumor Lysis Syndrome

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GENERAL

Emergencies occurring in patients with malignant disorders may be conveniently classified into three major groups: (1) those caused by mechanical pressure or obstruction resulting from the tumor mass; (2) metabolic or hormonal problems; and (3) those arising out of treatment-related complications. The major oncologic emergencies are listed in Table 1.

INTRODUCTION

The tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, hyperphosphatemia and secondary hypocalcemia, is a consequence of treatment-induced or spontaneous tumor cell death. It usually occurs a few hours to a few days after commencing cytotoxic chemotherapy for tumors with a high percentage of proliferating and drug-sensitive cells. Cell death leads to the release of potassium, phosphate, uric

Table 1: Oncologic emergencies

Structural-obstructive	Metabolic	Treatment-related
Superior vena cava syndrome	Hypercalcemia	Tumor lysis syndrome
Pericardial effusion/ tamponade	Hyponatremia-SIADH	Hemolytic uremic syndrome
Increased intracranial pressure	Hyponatremia-Na depletion	Neutropenia and sepsis
Spinal cord compression	Hyperuricemia	Pulmonary infiltrates
Neoplastic meningitis	Lactic acidosis	Typhlitis
Airway obstruction	Hypoglycemia	Hemorrhagic cystitis
Intestinal/biliary/ urinary obstr	Adrenal insufficiency infusion reactions	Human antibody

acid, and other purine metabolites into the systemic circulation. When the renal clearance of these chemical moieties is overwhelmed, hyperkalemia, hyperuricemia, hyperphosphatemia and secondary hypocalcemia results. Serum lactate dehydrogenase (LDH) levels are also often elevated concurrently. Uncontrolled TLS progresses to lactic acidosis and acute renal failure, and may end fatally.

TLS has been reported in association with a wide variety of tumors. It is most commonly seen in hematologic malignances with large, bulky adenopathy or high white blood cell counts, especially Burkitt's lymphoma[1-4]. A pan-European retrospective chart review identified TLS in 3.4% of patients with acute myeloid leukemia, 5.2% of patients with acute lymphocytic leukemia, and in 6.1% of patients with non-Hodgkin's lymphoma[5]. TLS occurs relatively rarely in solid tumors, possibly due to their longer doubling time, low growth fraction, and slow response to treatment[6].

Hyperuricemia is also frequently noted in patients with cancer as an isolated finding. The pan-European retrospective chart review quoted above identified hyperuricemia without TLS in 13.6% of cases, with TLS in an additional 5.3%[5].

TLS may also occur after ionizing radiation (including total body irradiation in the transplant setting), embolization, radiofrequency ablation, monoclonal antibody therapy, glucocorticoids, interferon and in the setting of hematopoietic stem cell transplantation[7]. Spontaneously occurring TLS is a result of ongoing cell death in a rapidly growing tumor.

Risk factors for the development of TLS are: (1) the presence of bulky adenopathy, hepatosplenomegaly or

a high leukocyte count, (2) elevated pretreatment uric acid, (3) compromised renal function, (4) the use of potentially nephrotoxic drugs, (5) lactic acidosis, (6) dehydration and (7) elevated pretreatment LDH (>1500 U/L), which reflects a high tumor burden.

PATHOGENESIS

Cell lysis with the release of intracellular contents at a rate that exceeds the kidney's capacity to clear them is the most important etiologic factor in TLS.

The release of intracellular potassium from dying cells is the principal cause of hyperkalemia. Falling adenosine triphosphate levels before actual cell lysis also causes the leakage of potassium from the intracellular compartment, and this may account for the fact that hypercalcemia is often the first sign of TLS.

Rapidly dividing tumor cells have a high nucleic acid turnover. The purine nucleotides, guanosine, and adenosine from the lysed tumor cells are catabolized in the liver, first to inosine, then to hypoxanthine and xanthine; and finally oxidised to uric acid. The hyperuricemia that results leads on to an increased uric acid excretion by the kidneys. Uric acid, having a pKa of 5.4, is poorly soluble in acidic urine. The luminal pH in the distal tubules and collecting ducts of the kidney is 5, and thus the uric acid is precipitated in these sites, causing intraluminal tubular obstruction, distinct interstitial inflammatory changes and acute renal failure.

Phosphates are major intracellular constituents. Some cancer cells, particularly lymphoid cells, have been reported to contain higher levels of phosphate than their normal counterparts[8]. Thus, hyperphosphatemia follows tumor cell lysis, results in hyperphosphaturia, and subsequent acute nephrocalcinosis (the precipitation of calcium phosphate crystals in the renal tubules). Elevated blood phosphate levels may not be observed until two days after beginning cytotoxic therapy. The elevation can exceed 20 mg/dl and persist for 4 to 5 days.

Hypocalcemia is the direct result of tissue precipitation of calcium phosphate. Hypocalcemia is also secondary to inappropriately low levels of plasma 1,25-dihydroxyvitamin D_3 (calcitriol)[9]. This hypocalcemia leads to increased levels of parathyroid hormone, with a resultant decrease in phosphate reabsorption in the proximal tubule, thus accentuating the hyperphosphaturia and enhancing the nephrocalcinosis.

Intravascular volume depletion; renal precipitation of nucleic acid metabolites, most notably uric acid; and acute nephrocalcinosis all contribute to the renal failure seen in TLS.

CLINICAL FEATURES

The clinical presentation ranges from asymptomatic laboratory abnormalities to catastrophic manifestations of the various electrolyte disturbances. Neuromuscular irritability, tetany, seizures and mental status changes are a consequence of hypocalcemia; cardiac arrhythmias and cardiac arrest result from hyperkalemia; acute renal failure is precipitated by hyperuricemia and hyperphosphatemia; and acute renal failure (plus lactic acidosis) leads on to a metabolic acidosis.

Hyperkalemia (>5 meq/L) is often the first sign of TLS, and this hyperkalemia poses the greatest immediate threat. In patients with high leucocyte and platelet counts, artificially elevated potassium levels ("pseudo-hyperkalemia") may be seen due to the lysis of these cells after the blood is drawn. Pseudohyperkalemia is usually recognized by the absence of electrocardiographic changes. Under such circumstances, immediate separation of plasma, and assay of plasma potassium instead of serum potassium may be practiced. Hyperkalemia is characterized by a variety of constitutional, cardiac and neuromuscular symptoms. Nausea, vomiting, diarrhea, muscle cramps, weakness and paresthesias are the important noncardiac manifestations. Electrocardiographic abnormalities such as peaked T waves and QRS widening are pointers towards the diagnosis. The severity of the ECG abnormalities parallels the severity of hyperkalemia. As hyperkalemia increases, the ECG shows increased T-wave amplitude, decreased R-wave amplitude, increased S-wave depth, prolongation of P-R interval, and widening of the QRS complex. Sinus node dysfunction, conduction disturbances and malignant arrhythmias are the major, potentially lethal consequences of hyperkalemia.

Hyperuricemia (>7 mg/dL), although not posing an immediate threat, is the most common finding. The resultant increased urinary excretion of the uric acid leads on to intraluminal tubular obstruction and acute hyperuricemic nephropathy, characterized by acute renal failure and a rapidly rising serum creatinine level. Blood uric acid level of more than 20 mg/dl is consistently associated with this form of renal impairment. Even lower levels can lead to a renal failure in the presence of acidosis or volume depletion. (The various other types of hyperuricemic nephropathy - gouty nephropathy, uric acid nephrolithiasis and interstitial nephritis of hyperuricemia are beyond the scope of this article). It must here be emphasized that serum samples obtained for uric acid should immediately be cooled to between 0°C and 4°C to prevent *ex vivo* enzymatic degradation of uric acid, which will lead to a falsely low level being reported.

Hyperphosphatemia (>4.5 mg/dl) by itself does not cause symptoms. Elevated blood phosphate levels may not be seen until 2 days after commencing cytotoxic chemotherapy. Such elevations can exceed 20 mg/dl and persist for 4 to 5 days. Renal damage and acute renal failure result from the precipitation of calcium phosphate in the kidney. Inordinate hypocalcemia (e.g., with alkalosis from bicarbonate administration or vomiting) can cause tetany.

Hypocalcemia (< 8 mg/dl), which occurs secondarily to hyperphosphatemia, manifests as muscle twitches, cramps, carpopedal spasm, paresthesia, and tetany. More severe symptoms, such as mental status changes, confusion, delirium, hallucinations, and seizures are sometimes seen. Severe hypocalcemia can complicate hyperkalemia and its associated cardiotoxicity.

DIAGNOSIS

A high index of clinical suspicion will usually ensure that the diagnosis of TLS is not overlooked. The finding of uric acid crystals in urine is strong evidence for uric acid nephropathy. The ratio of urinary uric acid to urinary creatinine is >1 in patients with acute hyperuricemic nephropathy, and <1 in renal failure due to other causes.

PREVENTION

The baseline measurement of blood urea nitrogen, creatinine, electrolytes, calcium, phosphate, and uric acid at presentation is the most effective guide towards preventive management. These preventive measures are undertaken to achieve a high urine flow, reduce the uric acid burden and minimize absorption of phosphate; thus increasing the elimination of potassium and minimizing the likelihood that uric acid and/or calcium phosphate will precipitate in renal tissue and tubules.

Prophylactic management should preferably begin 24 hours before the administration of chemotherapy. Vigorous hydration to achieve high urine flow, allopurinol therapy to reduce uric acid production, and oral phosphate binders to prevent their absorption are the key ingredients in preventing TLS (see below).

THERAPY

Aggressive hydration is the single most important intervention, and this should begin as soon as possible. Intravenous fluids are administered at a rate of 3000 ml/m^2/day so as to maintain a high urine output. When possible, tumor therapy should be delayed so that hydration can be administered. Alkalinization of the urine by the administration of bicarbonate is recommended to avoid crystallization of uric acid in the kidneys. However, it favors precipitation of calcium/phosphate complexes in renal tubules, which is of major concern in patients with concomitant hyperphosphatemia. Furthermore, the metabolic alkalemia that may result from the administration of bicarbonate can worsen the neurologic manifestations of hypocalcemia. Thus, alkalinization of the urine is not universally recommended, and requires great caution.

Hyperkalemia needs an aggressive multipronged approach. Cation exchange resins that bind potassium promote bowel elimination of phosphates. Kayexalate 15 to 30 g every 6 hours, along with 20 to 30 ml of 70% sorbitol (to help expel the resin from the bowel) is recommended. In patients without renal failure, loop diuretics augment the urinary excretion of excess potassium. Sodium bicarbonate 150 to 300 mEq iv corrects acidemia, and shifts potassium back into cells. Hypertonic dextrose infusion (50 to 100 ml of 50% solution) along with 10 units of regular insulin augments this process. Calcium gluconate antagonizes the cardiac effects of hyperkalemia and is particularly useful in the presence of concomitant hypocalcemia. 10 to 30 mL of a 10% solution provides immediate but transient benefit. In the presence of renal failure, hemodialysis will be necessary to correct the hyperkalemia.

Hyperphosphatemia and its resultant hypocalcemia should be managed with oral phosphate binders such as aluminum hydroxide, 30 ml four times a day. Extracellular volume expansion with the infusion of half-normal saline at 100 to 200 ml/hour is often beneficial. Administration of hypertonic dextrose and insulin can be used but are rarely needed. When blood phosphate levels are very high, 20% dextrose containing 10 units of regular insulin is infused at 50 to 100 ml/hour until the phosphate levels fall below 7 mg/dl. Because calcium administration can promote metastatic calcifications, it should be avoided except as needed in the management of hyperkalemia.

Hyperuricemia, which is central to the development of acute renal failure, needs immediate and aggressive therapy. Until recently, allopurinol has been the standard of treatment of hyperuricemia. Allopurinol (an analogue of the natural purine base hypoxanthine) and its metabolite, oxypurinol, inhibit xanthine oxidase, the enzyme responsible for converting hypoxanthine to xanthine and in turn to uric acid. Thus, both allopurinol and oxypurinol inhibit the formation of uric acid; however, neither has an effect on preexisting uric acid.

Oral allopurinol has a bioavailability of 50%, and In the management of patients with TLS is usually administered at a dose of 200 to 400 mg/m²/d, either as a single dose, or divided into three times a day, titrating the dose to achieve the desired level of serum uric acid. Intravenous allopurinol (available abroad at prohibitive costs!) may have a place in critically ill patients, and when oral administration is medically precluded because of emesis/bowel obstruction or other causes[10]. The doses of allopurinol should be adjusted for creatinine clearance as follows: 300 mg/d for a clearance greater than 20 ml/min; 200 mg/d for a clearance of 10 to 20 ml/min; 100 mg/d for a clearance of 3 to 10 ml/min; and 100 mg every 36 to 48 hours for a clearance less than 3 ml/min.

Therapy with allopurinol does have several limitations and drawbacks. Because both allopurinol and oxypurinol have no effect on preexisting uric acid, uric acid levels usually do not fall until after 48 to 72 hours of treatment. Also, inhibition of xanthine oxidase leads to increased plasma levels of hypoxanthine and xanthine, with increased renal excretion of both metabolic products. In the kidneys, hypoxanthine and especially xanthine (pKa = 7.4) get precipitated and contribute to the acute renal failure, rather than alleviating it. Hence, allopurinol may be ineffective in as many as 43% of patients with TLS. Allergic reactions such as skin rashes and urticaria are sometimes seen, and may necessitate withdrawal of the drug. The incidence of allergic reactions is increased in patients receiving amoxicillin, ampicillin, or thiazide diuretics. Finally, allopurinol can interfere with the metabolism of some chemotherapeutic agents.

Therefore, an alternate approach to the treatment of hyperuricemia is the use of the enzyme urate oxidase. Urate oxidase is found in most mammals but is not expressed in humans, a result of a nonsense mutation in the coding region during evolution[11]. Urate oxidase catalyzes the oxidation of uric acid to allantoin, a catabolite that is rapidly excreted by the kidneys[12]. Uricozyme, a nonrecombinant urate oxidase extracted from *Aspergillus flavus*, has been available in France and Italy for more than two decades for the treatment of hyperuricemia[13]. Recombinant urate oxidase, rasburicase (Fasturtec/Elitek) produced in *Saccharomyces cerevisiae* using a urate oxidase complementary DNA from *A flavus* has helped to overcome the nearly 5% hypersensitivity reactions seen with Uricozyme.

With urate oxidase, rapid reduction in uric acid occurs, without a buildup of precursors. In a majority of patients uric acid levels fall within 4 hours of rasburicase

injection to 0.5 to 1.0 mg/dL; and these levels are maintained throughout the treatment course. A small percentage of patients who received rasburicase and attained normal uric acid levels have nevertheless required dialysis. This observation is not unexpected, given the fact that rasburicase affects only one of several factors contributing to the renal failure.

The generally recommended dose of rasburicase is 0.15 to 0.20 mg/kg every 12 hours in the first two or three days and every 24 hours thereafter for a total of 5 days. However, a dose of 0.15 mg/kg every 24 hours is likely to be adequate in the overwhelming majority of patients[14]. Side effects include skin rash, mild nausea and vomiting, and rarely a hypersensitivity reaction including anaphylaxis. Circulating antibodies against rasburicase or its epitopes occur in approximately 10% to 20% of patients, but do not appear to have any blocking activity, and thus do not interfere with the efficacy[15]. However, retreatments are likely to increase the allergic reactions, in these patients. Rasburicase should not be given to patients with glucose-6-phosphate dehydrogenase deficiency because hydrogen peroxide, a by-product of the urate oxidase reaction, presents a burden to these patients that can lead to hemolysis.

The relative efficacy of rasburicase over allopurinol in preventing acute renal failure secondary to hyperuricemia is not clear. Some studies suggest that rasburicase can reduce the need for dialysis, while others report only clinically insignificant differences in serum creatinine between the two arms[15,16]. However, rasburicase's rapid onset of action and ability to lower preexisting elevated uric acid levels are distinct advantages. In patients with a rapidly proliferating chemosensitive tumor, this may permit the commencement of chemotherapy treatment without delay. However, rasburicase has no effect on the other manifestations of TLS, and these will necessarily need appropriate treatment.

If acute renal failure develops, Immediate hemodialysis is generally recommended. In the presence of TLS, serum chemistries should be monitored every 6 to 12 hours. Biochemical parameters that indicate the need for hemodialysis are: serum potassium >6.0 meq/L, serum uric acid >10 mg/dL, serum creatinine >10 mg/dl and serum phosphate >10 mg/dl or increasing. In addition, symptomatic hypocalcemia is also considered an indication for dialysis. conventional hemodialysis far more effective in eliminating uric acid and phosphate than peritoneal dialysis. In patients presenting with TLS hemodialysis must be started before cytotoxic therapy is administered. Hemofiltration offers a gradual,

continuous method of removing cellular byproducts and fluid.

PROGNOSIS

Established TLS is associated with a high morbidity and mortality. The pan-European retrospective chart review quoted earlier has reported an overall mortality of 17.5% for patients who developed TLS as against 0.9% for all patients in the series[5]. However, judicious prophylaxis can lead to successful treatment or even prevention. Renal functional recovery can be predicted after the uric acid level is reduced to < 10 mg/dl. A relatively higher mortality has been reported inpatients with solid tumors who develop TLS, when compared with patients with hematologic malignancies. This is likely a consequence of reduced awareness of the occurrence of this problem in solid tumors, and the consequent lesser attention paid to preemptive prophylactic measures.

SUGGESTED READING

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