A Focused Review of the Pathogenesis, Diagnosis, and Management of Tumor Lysis Syndrome for the Interventional Radiologist

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The tumor lysis syndrome (TLS) is one of the most frequently encountered and dangerous oncologic emergencies.¹ TLS describes a constellation of laboratory and clinical findings resulting from the rapid breakdown of tumor cells releasing their intracellular contents into the systemic circulation. It occurs most commonly in hematologic malignancies at the start of antineoplastic therapy, but has also been reported in a broad variety of solid organ malignancies, as well as occurring spontaneously without chemotherapy.^{2–5} As a potentially fatal oncologic emergency, it is imperative to identify patients at risk for early preventative therapy, understand the pathophysiology and consequences of this syndrome, and recognize the clinical and laboratory manifestations of TLS to ensure timely and appropriate treatment.

Case Report

A 35-year-old woman with no significant past medical history presented with several months of weight loss, night sweats, fatigue, and abdominal pain. A computed tomography of the abdomen and pelvis demonstrated a large abdominal mass as well as extensive retroperitoneal and thoracic lymphadenopathy. Excisional lymph node biopsy confirmed the diagnosis of diffuse large B cell lymphoma. Her laboratory evaluation at presentation was notable for leukocytosis, elevated serum lactate dehydrogenase (LDH), and an increased creatinine that subsequently improves with intravenous (IV) fluids. She was admitted to the hospital, aggressively hydrated with IV fluids, and given prophylactic allopurinol in preparation for induction chemotherapy. She was started on R-CHOP chemotherapy, a regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. One day after starting treatment, her potassium was noted to increase, for which she was treated with sodium polystyrene sulfonate, insulin, dextrose, and calcium gluconate. She also experi-

enced nausea, vomiting, and diarrhea after her chemotherapy that was treated with antiemetics and further hydration. Her serum uric acid began to increase 36 hours after induction chemotherapy, and allopurinol was changed to rasburicase. Her uric acid stabilized and eventually began to decrease; however, her serum phosphorus and creatinine continued to rise. Serum creatinine doubled in the course of several days despite aggressive IV hydration and her urine output began to decline. She was transferred to the intensive care unit and started on continuous hemodialysis. Over the following week, her renal function recovered, and she was taken off of hemodialysis and her electrolytes normalized.

Epidemiology

TLS occurs most commonly in patients with hematological malignancies, most notably in non-Hodgkin lymphoma (NHL) and acute lymphocytic leukemia (ALL); however, it has also been extensively reported in solid tumor malignancies.^{2,4,6} Tumor-specific risk factors include a large tumor burden, sensitivity of the tumor to chemotherapy, and rapid tumoral growth rate.^{6–8} Patient risk factors include high white blood cell count, elevated uric acid, impaired renal function, and elevated LDH before the initiation of cancer treatment.^{8–11} TLS most commonly develops after the initiation of chemotherapy, radiation therapy, or corticosteroids but has also been reported to occur spontaneously.^{3,5,12,13} In solid tumors, TLS seems to occur more commonly in those tumors that are more sensitive to chemotherapy; however, it has also been reported in tumors that are considered relatively insensitive to chemotherapy, such as melanoma, sarcoma, and hepatocellular carcinoma.⁴ Several case reports have also documented the development of TLS in patients with hepatocellular carcinoma following transarterial chemoembolization of large hepatic lesions.^{14,15}

The precise incidence of TLS is not well established, likely due to changing standards of care in prophylactic treatment as well as broad variations in the type of therapy and cancer cell mass.¹ In one case review study of 102 patients with intermediate to high-grade NHL, laboratory-defined TLS was observed in 42% of patients, while clinically significant symptoms requiring specific therapy occurred in only 6% of patients.¹¹ A larger study evaluating pediatric patients with NHL included 1,791 patients and reported an overall incidence of 4.4% developing TLS, although a higher incidence of 8.4% in a subset analysis of children with Burkitt lymphoma or B cell ALL was noted.¹⁶ In a European study that spanned four countries and included 722 pediatric and adult patients receiving induction treatment for ALL, acute myeloid leukemia (AML), and NHL, TLS (defined as either laboratory evidence of TLS or TLS requiring management) was observed in 5% of patients.¹⁷ In an additional cohort of 772 patients with AML undergoing chemotherapy, clinical TLS was observed in 5%, and laboratory TLS was seen in 12% of patients.⁹

Pathophysiology

The metabolic abnormalities of TLS result from the rapid destruction of large numbers of cancer cells and the release of their intracellular products into the blood stream. Electrolyte abnormalities such as hyperkalemia, hyperphosphatemia, and hypocalcemia result from the rapid release of intracellular potassium and phosphate, whereas hyperuricemia results from the breakdown of nucleic acids released from malignant cells.

Perhaps, one of the most dangerous and earliest consequences of TLS is hyperkalemia, caused by the release of large quantities of potassium into the extracellular fluid, which may often be further exacerbated by renal failure and acidosis.¹² Severe hyperkalemia causes potentially fatal ventricular dysrhythmias if not rapidly recognized and corrected. Hyperphosphatemia similarly results from release of intracellular phosphate, which is often present in far higher quantities in malignant cells than nonmalignant cells.¹⁸ Phosphate binds with calcium and precipitates in renal tubules, resulting in hypocalcemia, nephrocalcinosis, and acute renal failure.^{12,19,20}

Hyperuricemia usually develops 48 to 72 hours after the initiation of chemotherapy.¹⁸ Uric acid is a breakdown product of purine nucleic acids, which are present in large quantities in malignant cells due to their high rates of cell turnover.¹² Purine nucleotides are degraded into hypoxanthine, which is catabolized into xanthine and then uric acid. This process is catalyzed by xanthine oxidase, which is the therapeutic target of allopurinol (►Fig. 1). Uric acid then precipitates in the kidney forming uric acid crystals that can obstruct renal tubules. Elevated uric acid also contributes to renal failure independently of crystal formation through renal vasoconstriction, impairment of autoregulation, decreased renal blood flow, and inflammation.^{1,21} In patients treated with allopurinol, which blocks the catabolism of both hypoxanthine and xanthine, xanthine can also precipitate in renal tubules, sometimes forming stones and further contributing to renal failure.^{22–24}

Fig. 1 Purine nucleic acids are broken down into both hypoxanthine and xanthine. Allopurinol inhibits the formation of uric acid by inhibiting xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to xanthine, and xanthine to uric acid. Rasburicase is an analog of urate oxidase, which catalyzes the conversion of uric acid to allantoin.

Acute renal failure in TLS is a multifactorial process, resulting both directly from the metabolic derangements of TLS as well as from volume depletion due to gastrointestinal losses, high insensible losses, and poor appetite related to cancer and cancer therapy. In addition to hypovolemia being an independent risk factor in renal injury, the decrease in volume traversing the kidney along with an acidic pH further promote uric acid crystal formation.¹² Patients at risk for TLS may also be at higher risk of renal injury due to nephrotoxic antineoplastic or antimicrobial agents, periods of prolonged hypotension, and the use of contrast media.

Diagnosis and Classification

The most commonly used classification of TLS divides the syndrome into laboratory-defined TLS and clinical TLS. This approach was first proposed by Hande and Garrow in 1993 and was revised and updated by Cairo and Bishop in 2004.^{8,11} The Cairo and Bishop classification system is most commonly used now by the Children's Oncology Group and other research organizations.⁷

Laboratory TLS is defined in this classification system as the presence of two or more of the following laboratory makers being either above or below normal ranges, or 25% changed from baseline: increased uric acid, increased potassium, increased phosphorus, and decreased calcium⁸ (►Table 1). These laboratory changes also must occur 3 days before or 7 days after the initiation of chemotherapy, and assumes adequate hydration, alkalinization if appropriate, and administration of a hypouricemic agent.⁸

Clinical TLS is defined as the presence of laboratory TLS with one or more of the following: creatinine greater than 1.5

Table 1 The classification system for laboratory and clinical TLS proposed by Cairo and Bishop in 2004

Laboratory Tumor Lysis Syndrome	Clinical Tumor Lysis Syndrome
Presence of ≥ 2 of the following:	Presence of laboratory TLS plus any of the following:
Hyperuricemia or 25% increased from baseline	Creatinine ≥ 1.5 times the upper limit of normal
Hyperkalemia or 25% increased from baseline	Cardiac arrhythmia or sudden death
Hyperphosphatemia or 25% increased from baseline	Seizure
Hypocalcemia or 25% decreased from baseline	

Notes: The metabolic abnormalities defining laboratory TLS must occur 3 days before or 7 days after the initiation of chemotherapy, and assume adequate hydration, use of a hypouricemic agent, and alkalinization if appropriate. It is also assumed that clinical TLS defining changes in creatinine, cardiac arrhythmias/sudden death, and seizure are not directly or probably attributed to a therapeutic agent.

times the upper limit of normal, cardiac arrhythmia or sudden death, and seizure⁸ (► **Table 1**). The distinction of clinical TLS is meant to differentiate those patients with laboratory marker elevation from those with clinically significant life-threatening complications requiring specific therapies. Potential therapies include treatment of hyperkalemia, use of antiarrhythmics, and dialysis.

Prevention and Management

Prevention of TLS consists of using medications that decrease uric acid, and providing aggressive IV hydration before, during, and after antineoplastic treatment.^{1,7} Urinary alkalinization used to be commonly recommended as part of the preventative pretreatment of TLS, as increasing the urine pH makes uric acid more soluble and less likely to precipitate in the renal tubules. This practice is now relatively uncommon in part because of data suggesting that hydration with saline alone is equally effective as alkalinization in decreasing uric acid precipitation, and also because alkalinizing the urine may promote calcium phosphate deposition in patients with severe hyperphosphatemia.²⁵

Allopurinol is a competitive inhibitor of xanthine oxidase, an enzyme responsible for the catabolism of hypoxanthine to xanthine, and xanthine to uric acid. It was first reported in 1966 to reduce uric acid in patients undergoing chemotherapy and remains the most widely used hypouricemic agent.²⁶ While effective at preventing new uric acid formation, allopurinol suffers from two important limitations. First, inhibition of xanthine oxidase may lead to a buildup of xanthine, which can form crystals that deposit in the kidney leading to xanthine nephropathy.^{22–24} More importantly, allopurinol is effective only in prevention of uric acid formation but is not effective in reducing existing uric acid burden.

Rasburicase is a pure recombinant form of urate oxidase, an enzyme that catalyzes the oxidation of uric acid into allantoin—a much more soluble and readily excretable substance.^{27,28} Numerous clinical trials have shown that rasburicase is safe and effective in decreasing serum uric acid levels in leukemia and lymphoma patients being given antineoplastic therapy.^{28–32} In a cohort of 131 pediatric and young adult patients, newly diagnosed with leukemia or lymphoma who were pretreated with rasburicase, uric acid levels decreased and remained low in patients with or without hyperuricemia at presentation, and serum creatinine was also shown to

significantly decrease after treatment—returning to a normal level in all patients.²⁸ A cohort of 100 adult patients with NHL demonstrated similar benefits of rasburicase, with all patients showing decreases in uric acid levels that remained low during chemotherapy and with no patient developing renal failure.²⁹

Comparative trials between allopurinol and rasburicase have demonstrated more dramatic reductions in serum uric acid and other chemistry markers with rasburicase; however, possibly due to the rarity of clinical TLS, it has been difficult to demonstrate a difference in clinical TLS, renal failure, or mortality.^{27,33–35} In a randomized control trial of 52 pediatric patients with leukemia and lymphoma receiving either allopurinol or rasburicase, patients receiving rasburicase had a more rapid decline in uric acid and maintained lower levels of uric acid throughout their therapy, though sample sizes were too small to determine whether this corresponded to a clinical difference in renal outcomes or development of TLS.²⁷ Another randomized controlled trial compared the efficacy of rasburicase, rasburicase followed by allopurinol, and allopurinol alone in 275 adult patients with hematologic malignancies undergoing chemotherapy. This trial similarly found that rasburicase produced more rapid decreases in uric acid levels than allopurinol; however, no difference was seen in development of clinical TLS, which occurred rarely—only four times in the allopurinol alone group and three times in each of the other two groups.³³ A Cochrane review on the subject similarly concluded that while rasburicase may be effective in decreasing uric acid, it is unclear whether it is more beneficial than allopurinol in reducing clinical TLS, renal failure, or mortality.³⁵

With the availability of new hypouricemic agents, further risk classification is required to decide how to pretreat patients undergoing chemotherapy. An expert panel on TLS published a risk classification system that incorporated both hematologic and solid tumor malignancies in 2008, which was further refined in 2010.^{6,7} In this risk assessment model, most solid tumors are classified as low risk. Only a few rare solid tumors, such as neuroblastomas, germ cell tumors, small cell lung cancers, and those with bulky or advanced stage diseases, are potentially classified as intermediate risk. Multiple myeloma, chronic myelogenous leukemia, indolent NHL, Hodgkin lymphoma, and chronic lymphocytic leukemia are also classified as low risk. AML, ALL, NHLs, and all other leukemias and lymphomas are individually risk stratified

based on their presenting stage, pretreatment uric acid level, leukocyte count, LDH, potassium, phosphate, and presence of renal dysfunction.^{6,9} Intermediate-risk patients with renal dysfunction, hyperuricemia, hyperkalemia, or hyperphosphatemia are also moved to the high-risk category.⁶

After risk stratifying patients to low, intermediate, or high risk, the expert panel further recommended pretreating low-risk patients with hydration with or without allopurinol, intermediate-risk patients with hydration and allopurinol, and high-risk patients with hydration and rasburicase. All patients should also have frequent electrolyte and serum chemistry monitoring, and if any low- or intermediate-risk patients develop laboratory TLS, their hypouricemic therapy should be changed to rasburicase.⁶

Does Surgical Tumor Debulking Decrease the Risk for Tumor Lysis Syndrome?

It is known that the presence of a large tumor mass increases the risk for TLS, and the question has been posed whether surgically debulking the mass of the tumor before chemotherapy reduces the risk of TLS. Although no large trial exists to evaluate this specific question, evidence available from smaller studies and case reports suggests that debulking is not an effective strategy to reduce the risk of TLS, likely due to delays in induction chemotherapy, risk of surgical complication including intraoperative TLS, and rapid tumor regrowth.^{36–38} In patients with widespread Burkitt lymphoma, resection of large amounts of tumor has not been shown to increase survival, though there may be some benefit of resection in select cases with localized disease.^{38,39} In addition to patients being at risk for surgical complications, intraoperative TLS has also been reported to occur in a patient with Burkitt lymphoma undergoing staging laparotomy, suggesting that surgery itself may be a trigger for TLS.³⁷ Finally, debulking surgery may not be of benefit due to rapid tumor regrowth leading to TLS, as demonstrated in a case report of a patient with a gastrointestinal stromal tumor who underwent surgical debulking to control abdominal pain. During his surgery, his tyrosine kinase inhibitor was held and in the absence of his therapy, the tumor regrew quickly; by the time the patient recovered from his debulking surgery, the mass had grown to again occupy the majority of his pelvis. After resuming his systemic therapy, this patient suffered from clinical TLS.³⁶

Despite significant advances in the identification and management of TLS, this potentially fatal syndrome remains one of the most common oncologic emergencies. Extensive study of patients with hematologic malignancies has improved the ability to identify patients at increased risk and to initiate preventative therapy, though identification of patients at high risk of solid organ TLS and spontaneous TLS remains challenging. A deeper understanding of the pathophysiology of this syndrome and the development of novel more efficacious therapies has also led to improved outcome for these patients. Despite these advancements and improvements, TLS remains a common and important oncologic emergency for every provider

involved in the care of cancer patients to rapidly recognize and appropriately treat.

References

- Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med* 2011;364(19):1844–1854
- Mirrakhimov AE, Ali AM, Khan M, Barbaryan A. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors* 2014;6(2):5389
- Vaisban E, Braester A, Mosenzon O, Kolin M, Horn Y. Spontaneous tumor lysis syndrome in solid tumors: really a rare condition? *Am J Med Sci* 2003;325(1):38–40
- Baeksgaard L, Sørensen JB. Acute tumor lysis syndrome in solid tumors—a case report and review of the literature. *Cancer Chemother Pharmacol* 2003;51(3):187–192
- Jasek AM, Day HJ. Acute spontaneous tumor lysis syndrome. *Am J Hematol* 1994;47(2):129–131
- Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol* 2010;149(4):578–586
- Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008;26(16):2767–2778
- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127(1):3–11
- Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica* 2008;93(1):67–74
- Mato AR, Riccio BE, Qin L, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. *Leuk Lymphoma* 2006;47(5):877–883
- Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med* 1993;94(2):133–139
- Davidson MB, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 2004;116(8):546–554
- Sklar NT, Markham M. Spontaneous recurrent tumor lysis syndrome in breast cancer. *Am J Clin Oncol* 1995;18(1):71–73
- Hsieh PM, Hung KC, Chen YS. Tumor lysis syndrome after transarterial chemoembolization of hepatocellular carcinoma: case reports and literature review. *World J Gastroenterol* 2009;15(37):4726–4728
- Tsai WL, Liang PC, Chen CH. Tumor lysis syndrome after transarterial chemoembolization plus portal venous embolization for hepatocellular carcinoma. *J Formos Med Assoc* 2012;111(12):724–725
- Wössmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. *Ann Hematol* 2003;82(3):160–165
- Annemans L, Moeremans K, Lamotte M, et al. Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. *Leuk Lymphoma* 2003;44(1):77–83
- Flombaum CD. Metabolic emergencies in the cancer patient. *Semin Oncol* 2000;27(3):322–334
- Boles JM, Dutel JL, Briere J, et al. Acute renal failure caused by extreme hyperphosphatemia after chemotherapy of an acute lymphoblastic leukemia. *Cancer* 1984;53(11):2425–2429

- 20 Kanfer A, Richet G, Roland J, Chatelet F. Extreme hyperphosphataemia causing acute anuric nephrocalcinosis in lymphosarcoma. *BMJ* 1979;1(6174):1320–1321
- 21 Shimada M, Johnson RJ, May WS Jr, et al. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. *Nephrol Dial Transplant* 2009;24(10):2960–2964
- 22 Greene ML, Fujimoto WY, Seegmiller JE. Urinary xanthine stones—a rare complications of allopurinol therapy. *N Engl J Med* 1969;280(8):426–427
- 23 LaRosa C, McMullen L, Bakdash S, et al. Acute renal failure from xanthine nephropathy during management of acute leukemia. *Pediatr Nephrol* 2007;22(1):132–135
- 24 Pais VM Jr, Lowe G, Lallas CD, Preminger GM, Assimos DG. Xanthine urolithiasis. *Urology* 2006;67(5):1084.e9–1084.11
- 25 Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. *J Clin Invest* 1977;59(5):786–793
- 26 DeConti RC, Calabresi P. Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. *N Engl J Med* 1966;274(9):481–486
- 27 Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001;97(10):2998–3003
- 28 Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients With leukemia or lymphoma. *J Clin Oncol* 2001;19(3):697–704
- 29 Coiffier B, Mounier N, Bologna S, et al; Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003;21(23):4402–4406
- 30 Jeha S, Kantarjian H, Irwin D, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. *Leukemia* 2005;19(1):34–38
- 31 Bosly A, Sonet A, Pinkerton CR, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. *Cancer* 2003;98(5):1048–1054
- 32 Galaray PJ, Hochberg J, Perkins SL, Harrison L, Goldman S, Cairo MS. Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: a Children's Oncology Group Report. *Br J Haematol* 2013;163(3):365–372
- 33 Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—results of a multicenter phase III study. *J Clin Oncol* 2010;28(27):4207–4213
- 34 Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. *Am J Kidney Dis* 2013;62(3):481–492
- 35 Cheuk DK, Chiang AK, Chan GC, Ha SY. Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer. *Cochrane Database Syst Rev* 2014;8:CD006945
- 36 Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007;25(23):3544–3546
- 37 Lee MH, Cheng KI, Jang RC, Hsu JH, Dai ZK, Wu JR. Tumour lysis syndrome developing during an operation. *Anaesthesia* 2007;62(1):85–87
- 38 Stein JE, Schwenn MR, Jacir NN, Harris BH. Surgical restraint in Burkitt's lymphoma in children. *J Pediatr Surg* 1991;26(11):1273–1275
- 39 Stovroff MC, Coran AG, Hutchinson RJ. The role of surgery in American Burkitt's lymphoma in children. *J Pediatr Surg* 1991;26(10):1235–1238