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REVIEW

Current understanding of tumor lysis syndrome

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Abstract

Tumor lysis syndrome (TLS) is an oncologic emergency from the intracellular release of material in lysing malignant cells. The earlier it is treated, the less likely it is to be harmful to an individual and spread through the body. Common complications of TLS include arrhythmias, which are caused by hypocalcemia or hyperkalemia, renal failures due to hyperuricemia or hyperphosphatemia, and seizures. Furthermore, the risk to develop TLS varies widely based on several factors including factors that are related to disease, the patient, and the treatment of the patient. Laboratory data can be used to gauge the severity of TLS based on patient serum levels for specific markers. On the contrary, evidence of TLS via radiological imaging and electrocardiogram findings has been a limited way to evaluate TLS, indicating the need for further research in this area. Common trends of treatment have also been seen in the past several years, evident by case studies seen in the following literature review.

KEYWORDS
allopurinol, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, rasburicase, tumor lysis syndrome

1 | INTRODUCTION

Tumor lysis syndrome (TLS) is known as the most common disease-related hematologic cancer emergency in both adults and children.[1-5] Initially, it was found in patients with non-Hodgkin lymphoma or acute leukemia but since has become increasingly more common and prevalent.[1,6-9] TLS occurs due to a burst of tumor cells leading to a large release of potassium, phosphate, and nucleic acids into circulation, causing a significant amount of damage to the systemic circulation of the human body.[10] Studies have also shown that acute TLS (ATLS) can occur, causing a formation of emboli as a result of nuclear and cytoplasmic debris, resulting in mechanical obstruction of capillary beds, as seen in mouse models.[11] However, TLS rarely occurs in patients that have solid tumors,[12-15] and there have only been 74 cases reported between 1977 and 2011,[6,12,16-23] indicating their low risk and prevalence. Table 1 goes over the solid tumor types.[6,12-23] One type of TLS is called spontaneous TLS (STLS), which is a complicated form of TLS where cells are rapidly destroyed and lyse spontaneously without any therapeutic intervention such as chemotherapy to potentially induce this destruction.[24]

Despite the low risk and scarcity of these tumors, following therapy (ie., radiation, corticosteroids, and chemotherapy), TLS is more likely to develop, especially in gastric, lung, and breast cancer patients.[3,19,25-32] Several consequences can arise from the release of potassium, phosphate, and nucleic acids into circulation. For instance, when the nucleic acids are ultimately broken down to uric acid, this can lead to precipitation of uric acid in the renal tubules, renal vasoconstriction, impaired autoregulation, decreased renal blood flow, and inflammation.[10,33-35]

Several factors are involved in the onset of TLS. Patients may have high-grade lymphomas and acute lymphoblastic leukemia. If these patients have cytotoxic therapy to treat their diseases, TLS can occur.[10] Other factors include tumors that are highly sensitive to cytotoxic therapy or a high proliferative rate, making it more likely that it will burst and cause TLS.[10] Indicators for at-risk patients include proliferating tumors, bulky malignancies, large areas of tumor necrosis

TABLE 1 Solid tumors[6,12-23]

Breast cancer
Small cell lung cancer
Germ cell tumor
Melanoma
Merkel cell carcinoma
Head and neck cancer
Non-small cell lung cancer
Ovarian cancer
Vulva cancer
Prostate cancer
Hepatocellular carcinoma
Colorectal cancer
Gastric cancer
Sarcoma
Neuroblastoma
Medulloblastoma
Hepatoblastoma
Gestational trophoblastic neoplasia
Renal cell carcinoma
Transitional cell carcinoma
Thymoma

posttherapy, and elevated serum phosphorus, potassium, and uric acid levels.[36,37]

In attempts of treating diseases including chronic lymphocytic leukemia (CLL), newer treatment options using a B-cell lymphoma-2 protein inhibitor, venetoclax and oral kinase inhibitors, idelalisib, and ibrutinib have been used.[38] These therapies are a potential risk to lead to TLS due to the extreme sensitivity of these treatments and the rapid growth of the tumor. Furthermore, it usually occurs in the first cycle of therapy. To avoid TLS due to these therapies, it is recommended to monitor patients that are at high risk every 4 to 6 hours, patients that are at medium risk every 8 to 12 hours, and low-risk patients daily following the initiation of these newer therapeutic methods.[1,38] In addition, proper hydration, management of electrolytes, and oral hypouricemic agents such as allopurinol can be preventive measures.[38-40]

Herein, we review the physiology, clinical manifestations, laboratory diagnostics, radiological studies, and case studies of TLS to develop a core understanding of the condition and the risks associated with it.

2 | PHYSIOLOGY OF TLS

TLS has the potential to cause several harms as it develops from cytotoxic chemotherapy, large tumors, or radiation. When the tumor cells lyse, a significant amount of intracellular contents spill into the body's systemic circulation including potassium, phosphate, and nucleic acids, leading to complications such as hyperkalemia, hyperphosphatemia, secondary hypocalcemia, hyperuricemia, and acute kidney injury.[10]

The most common complications of TLS are arrhythmias and renal failure. Arrhythmias are caused by hypocalcemia or hyperkalemia while renal failure stems from hyperuricemia or hyperphosphatemia.[41] Over the first 12 to 24 hours of TLS, hyperkalemia occurs, as there is an efflux of potassium to the outside of the cell due to exceptionally rapid ATP consumption. No ATP remains for the Na+/K+ ATPase, and the ATP will merely leave the cell.[41-44] Hyperkalemia is the most impactful and dangerous component of TLS because this can lead to cardiac dysrhythmia.[1] In hyperphosphatemia, there is a release of phosphates from lysed cells and phosphates in the malignant cells will be elevated up to four times the normal amount, and this usually occurs 24 to 48 hours following therapy initiation.[41,45] This will lead to precipitation in the renal tubules and calcium phosphate salt formation, potentially leading to secondary hypocalcemia.[10] Furthermore, 48 to 72 hours following the onset of treatment, hyperuricemia often occurs, causing a significant secretion of uric acid into the renal tubules following kidney filtration, ultimately leading to renal failure.[41,45] Hypoxanthine is a result of the purine nucleic acids being catabolized into hypoxanthine and xanthine being and then to uric acid through xanthine oxidase. Acute kidney injury occurs because uric acid is poorly soluble, and when it is overly excreted, it leads to crystal precipitation and deposition into the renal tubules. However, hyperuricemia is no longer as involved in TLS as it once was, because of the wide use of allopurinol and rasburicase.[10,46,47] It is also important to note that hyperkalemia and hypocalcemia can lead to cardiac arrhythmia and arrest.[36] In essence, as a result of the electrolyte imbalances and abnormalities, multiple organ systems can potentially be dysfunctional or shut down, impacting the kidneys, heart, skeletal muscle, and the central nervous system.[48] Symptoms of central nervous system toxicity and dysfunction include seizures, psychiatric complaints, QT prolongation, and muscle tetany.[49,50]

Of all the harmful results from the lysis of cancer cells rich in potassium, phosphorous, and uric acid, hyperkalemia is one of the most potent due to adverse effects on skeletal muscle and cardiac myocardium.[49,51,52] Furthermore, hyperkalemia can also lead to several different types of electrocardiogram (ECG) abnormalities that include peaked narrow T waves, prolongations of PR and QRS intervals, and ultimately ventricular tachyarrhythmia and death.[49,53] In addition, past studies on hypouricemia in 78 patients with TLS showed that gout flare was not a result.[54]

3 | CLINICAL MANIFESTATIONS OF TLS

Several symptoms may show a potential onset of TLS. Since 2008, a specific set of guidelines show how to prevent and manage TLS, which has since been edited.[3,10,39] Table 2 presents a risk stratification system that utilizes the type of malignancy, the burden of disease, treatment, expected response to treatment, and renal function.[3,39] The risk is based on several factors, including age, type and stage of cancer, lactate dehydrogenase (LDH) level, white blood cell (WBC) count, and

TABLE 2 Symptoms associated with low, intermediate, and high risk of tumor lysis syndrome[3,10]

Low Risk (<1% Chance)	Intermediate Risk (1%-5% Chance)	High Risk (>5% Chance)
Acute myeloid lymphoma (AML) with white blood cell (WBC) count <25 000/microL and serum LDH level <2X upper limit of normal (ULN)	Adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma with an ULN serum LDH level above ULN that does not have a bulky disease	All Burkitt leukemia, stage III or IV Burkitt lymphoma or early stage Burkitt lymphoma with serum LDH level ≥2X ULN
Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with a WBC count ≤50 000/microL and not treated with fludarabine/rituximab or venetoclax	Stage III or IV childhood anaplastic large cell lymphoma with serum LDH level <2X ULN	ALL with WBC count ≥100 000 per microL and/or serum LDH level ≥2X ULN
Multiple myeloma and chronic myelogenous leukemia (CML)	Stage III or IV childhood diffuse large B-cell lymphoma with serum LDH level ≥2X ULN	AML with WBC count ≥100 000 per microL
Other types of adult non-Hodgkin lymphomas that do not meet the high risk or intermediate risk thresholds. Normal limit serum LDH level is required in this case.	Early stage Burkitt lymphoma with serum LDH level <2X ULN	Stage III or IV lymphoblastic lymphoma or early stage lymphoblastic lymphoma with serum LDH level ≥2X ULN
Other solid tumors in the body	Acute lymphoblastic leukemia (ALL) with WBC <100 000/microL and serum LDH level <2X ULN	CLL treated with venetoclax and lymph nodes ≥10 cm or lymph nodes ≥5 cm and absolute lymphocyte count ≥25 × 109/L, and an elevated level of serum uric
	AML with WBC 25 000 to 100 000/microL or AML with WBC < 25 000/microL and LDH ≥2X ULN	Adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma with serum LDH level above the ULN and a bulky tumor mass
	Early stage lymphoblastic lymphoma with serum LDH level <2X ULN	Stage III or IV childhood diffuse large B-cell lymphoma with serum LDH level ≥2X ULN
	CLL/SLL treated with fludarabine, rituximab, or lenalidomide, or venetoclax with lymph nodes ≥5 cm or an absolute lymphocyte count ≥25 × 109/L, and/or those with a high WBC count (≥50 000/microL)	
	Rare bulky solid tumors that are highly sensitive to chemotherapy (such as neuroblastoma, germ cell cancer, and small cell lung cancer)	

patient comorbidity.[55] In addition, the risks are split between low risk, which is a less than 1% chance of developing TLS; intermediate risk, which is a 1%-5% chance of developing TLS; and high risk, which is greater than a 5% chance of developing TLS.[3,39] TLS has also been more common in cancers that are associated with metastatic colon cancer such as endometrial cancer, hepatocellular carcinoma, CLL, and chronic myelogenous leukemia.[1,6-9,56-59] These patients often show chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine.[1] Furthermore, cytokine release syndrome (CRS) is a severe toxicity that is associated with chimeric antigen receptor T cells (ie, CAR T cells), which, when released on tumor cells, can lead to damage by reacting with proteins not present on the tumor cells. Furthermore, CRS has been shown to lead to TLS prior to conditioning with chemotherapy.[60]

Many symptoms of TLS are a product of the hyperkalemia, hyperphosphatemia, and hypocalcemia. The symptoms for TLS include nausea, vomiting, diarrhea, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and risk of sudden death.[10,39] While uric acid crystals can also form, they are usually not harmful because there is no output from the obstructed nephrons. TLS patients with hypocalcemia may have muscular activations such as spasms, a prolonged QT interval on the ECG, and mental disturbances.[49,50] TLS patients that have hyperkalemia may exhibit ECG abnormalities[53] and symptoms of cardiac arrest.

It is important to note that TLS can occur before the diagnosis of cancer. Therefore, it is vital to differentiate TLS from other diseases such as sepsis, obstructive renal disease, medication toxicities, use of contrast dye for imaging, and rhabdomyolysis. A thorough clinical diagnosis is necessary when patients are diagnosed with cancer comorbid with an acute decline in the function of their kidneys.[49,61] This testing should include urinalysis and urine microscopy, comprehensive metabolic panel, serum uric acid and LDH levels, complete blood count, and renal ultrasound.[49]

It is important to distinguish TLS from other inflammatory disorders that have similar clinical signs and symptoms. For example, congenital rubella syndrome (CRS) is due to the rubella virus infection during pregnancy, potentially leading to infants that have congenital malformations.[62,63] Despite the fact that rubella can be avoided through pregnancy, there are still cases throughout the world.[62] CRS is also geared more towards children and can lead to congenital defects including deafness and cataracts, distinguishable from TLS.[64,65] Another similar inflammatory disorder is sepsis, which is one of the most common reasons for hospitalization.[66,67] Similar to TLS, early interventions including antibiotic therapy and improve outcomes.[66,68,69] In addition, there are dysfunctions for multiple organs and a systemic inflammatory response syndrome (SIRS).[66] However, in sepsis, there is potential for septic shock, which is the need for vasopressors to keep the mean arterial pressure at >65 mmHg and lactate[66] levels >2 mmol/L. One major hyperinflammatory disease that has similar presentations to TLS is hemophagocytic lymphohistiocytosis (HLH). The trigger of HLH is usually infection and defects of natural killer cells and cytotoxic T cells.[70] Similar to TLS, early recognition is critical and treatment includes chemotherapy as well as immunosuppression. In addition, LDH levels are also markedly higher in HLH.[70]

4 | LABORATORY DIAGNOSIS OF TLS

Cairo-Bishop has developed specific laboratory criteria and guidelines to define TLS in terms of its severity based on the degree of serum creatinine elevation, the presence of and type of cardiac arrhythmia, and the presence and severity of seizures.[41,71] If there are two or more of any of a specific criterion of abnormalities in the body, one can be diagnosed with laboratory TLS. This includes a serum uric acid level ≥8 mg/dL, or a 25% increase from baseline; a serum potassium level ≥6 mmol/L, or a 25% increase from baseline; serum phosphate levels ≥6.5 mg/dL in children and ≥4.5 mg/dL in adults, or a 25% increase from baseline; and a serum calcium level ≤7 mg/dL, or a 25% decrease from baseline. In addition, these abnormalities must have occurred 3 days prior to or within 7 days following the beginning of chemotherapy treatment.[41,71] There is also a grading system to understand the severity of clinical TLS ranging from zero to five. This rating is based on serum creatinine, cardiac arrhythmia presence and type, and seizure presence and severity.[10,72] Table 3 outlines the criteria for the Cairo-Bishop grading of clinical TLS.[49,71]

There is an additional clinical definition of TLS that includes two of the aforementioned criteria as well as at least a serum creatinine level ≥1.5 times the upper limit of normal, or the development of cardiac arrhythmia or sudden death, or seizures.[41,71] Furthermore, in the year 2011, Howard et al refined TLS criteria to include two metabolic abnormalities in a 24-hour period 3 days prior to or within 7 days following treatment, a change from 25% to baseline in the

TABLE 3 Cairo-Bishop grading of clinical tumor lysis syndrome[49,71]

Variable	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine	None	1.5 times ULN and a rise that is not due to chemotherapeutic agents (applicable to grades 1-4)	>1.5-6.0 times the ULN	>3.0-6.0 times the ULN	>6.0 times ULN	Death
Cardiac arrhythmia	None	No intervention is indicated	Nonurgent medical intervention is indicated	Symptomatic and incompletely controlled or medically controlled or controlled with a device. The cardiac arrhythmias are not due to chemotherapeutic agents.	Life-threatening. Cardiac arrhythmias are not attributable to chemotherapeutic agents.	Death
Seizures	None	N/A	A brief generalized seizure and seizures that are well controlled with use of anticonvulsants or focal motor seizures that are infrequent and do not interfere with ADL	A seizure where consciousness is altered or is poorly controlled	A prolonged seizure	Death

TABLE 4 Studies on tumor lysis syndrome and its course of treatment[1,12,92-95]

Study	Clinical Manifestations	Laboratory Findings	History of Patient	Physician Diagnosis	Treatment	Outcome	Radiological Results
Kekre et al[92]	76-year-old man with constant nausea, vomiting, diarrhea, and decreased appetite for 3 weeks, elevated LDH level, hypocalcemia, hyperphosphatemia, and hyperkalemia	Not provided	Hemochromatosis complicated by arthritis, diabetes, class III chronic kidney disease, hypertension, dyslipidemia and erectile dysfunction, previous smoker	Hyperglycemic hyperosmolar state due to high glucometer reading (>30-mmol/L blood glucose reading) with serum calcium, phosphate, magnesium liver enzymes, and renal function tests not supporting this claim	IV fluid and insulin with calcium gluconate to treat hyperkalemia	Asterixis, confusion, and anuria with persistent hyperkalemia immediately developed. Patient went through dialysis without fluid removal and had profound shock two hours after dialysis, requiring vasopressors. Patient ultimately died in the ICU.	Computed tomography of abdomen displayed large hepatic mass. Autopsy displayed tumor measured at 19.2 × 11.0 × 8.0 cm in right hepatic lobe with an extension into hepatic portal vein. No evidence of iron deposition in liver.
Sommerhalder et al[93]	49-year-old African-American woman presenting with abdominal pain, nausea, vomiting, loss of appetite, early satiety, and subjective weight loss, postprandial abdominal pain in the upper right quadrant. The patient also had increasing edema of bilateral extremities associated with worsening dyspnea.	White blood cells: 12.14 × 103/μL; hemoglobin: 8.0 g/dL; platelets: 512 × 103/μL; potassium: 3.5 mmol/L; serum creatinine (Cr): 0.87 mg/dL; albumin: 2.7 g/dL; total bilirubin: 0.9 mg/dL; alanine aminotransferase: 57 U/L; aspartate aminotransferase: 212 U/L; alkaline phosphatase: 324 U/L; and a lactic acid: 2.3 mmol/L	Hypertension, gastroesophageal reflux, hyperlipidemia, and anemia, a 2011 cholecystectomy, maternal grandmother diagnosed with breast cancer at age 62	Patient was found to be in tumor lysis with lactate dehydrogenase levels: 10 853 U/L; uric acid: 20.3 mg/dL; and serum creatinine: 3.9 mg/dL.	Allopurinol, intravenous fluids, rasburicase, and dialysis treatments were initiated	Patient died following failure of multiple organs.	Computerized tomography (CT) scan of the abdomen and pelvis revealed hepatomegaly of 27.5 × 14.5 cm anteroposterior diameter with multiple hypo-attenuating lesions and with thickening of the cecum. Radiological liver biopsy demonstrated metastatic adenocarcinoma.
Howard et al[1]	8-year old boy initially with increased snoring, fatigue, sore throat, enlarged tonsils, and gradually increasing painless and nontender cervical lymphadenopathy. Returned to ER with vomiting,	White-cell count of 84 600 per cubic millimeter, with circulating lymphoblasts; a sodium level of 133 mmol/L; potassium, 5.9 mmol/L; bicarbonate, 16 mmol/L; creatinine, 1.0 mg/dL (88.4	Not provided	Nasal congestion, enlarged tonsils at the midline, significant anterior and posterior cervical adenopathy.	Initially, dexamethasone (4 mg) was administered intramuscularly, and loratadine was prescribed. At second visit, patient was given two boluses of normal saline (20 mL/kg of	Patient did not require dialysis and remains in remission after 5 years of diagnosis.	Chest radiography revealed minor mediastinal mass

(Continues)

TABLE 4 (Continued)

Study	Clinical Manifestations	Laboratory Findings	History of Patient	Physician Diagnosis	Treatment	Outcome	Radiological Results
	development of malaise, and moderate dehydration. Secondary complications included oliguria, hyperphosphatemia, an increased creatinine, and hypertension.	μmol/L); phosphorus, 8.5 mg/dL (2.7 mmol/L); calcium, 6.7 mg/dL (1.7 mmol/L); uric acid, 12.3 mg/dL (732 μmol/L); and lactate dehydrogenase, 4233 IU/L.			body weight), rasburicase (0.15 mg/kg) and 800 mg of aluminum hydroxide; intravenous fluids (2500 mL/m^2 of body-surface area) were administered daily. Patient was admitted to the ICU and T-cell acute lymphoblastic leukemia was diagnosed.		
Shenoy et al[94]	6-month old male infant with fever and loose stool since approximately 1 month of age. Loose stools were watery and black in color. Examination showed weak cry and decreased activity. Patient showed a high temperature at 101°C, pulse rate was 160 bpm, blood pressure 88/60 mmHg, and respiratory rate 62 per minute. Soft abdomen. Stool showed blood, urine showed protein and blood traces and urine microscopy showed uric acid crystals.	LDH 6192 IU/L, uric acid 18.2 mg/dL, PT 17.7, INR 1.21, creatinine 2.1 mg/dL, urea 115 mg/dL, calcium 5.9 mg/dL, phosphorus 5.4 mg/dL, sodium 131 mEq/L, potassium 3.6 mEq/L, bicarbonate 10.9 mEq/L, chloride 99 mEq/L, total bilirubin 0.3 mg/dL, total protein 4.9 g/dL, albumin 2.8 g/dL, AST 80 U/L, ALT 21 U/L, ALP 109 U/L.	Reduced feeding and decreased urine output. Child born by normal vaginal delivery at 9 months and has attained appropriate milestones for his age.	Bone marrow aspiration cytology was advised but could not be performed due to insufficient sample. Infant was ultimately diagnosed with acute myeloid lymphoma complicated with TLS and acute renal failure.	IV fluids and antibiotics and packed cell and platelet transfusion. Treatment with allopurinol to reduce uric acid levels and chemotherapy	Infant succumbed to death	Ultrasonographic examination of abdomen showed presence of bulky bilateral kidneys and fluid in hepatorenal pouch.
Kim et al[12]			Not provided				

(Continues)

TABLE 4 (Continued)

Study	Clinical Manifestations	Laboratory Findings	History of Patient	Physician Diagnosis	Treatment	Outcome	Radiological Results
	59-year-old man with abdominal distension and dyspepsia. There was also a protruding mass found in the colon. Following chemotherapy, patient had abdominal fullness and there was a metastases of the hepatic and abdominal lymph nodes.	Three days after starting the second cycle of FOLFOX chemotherapy, his blood urea nitrogen was 21.8 mg/dL (normal range, 8.0 to 23.0 mg/dL), creatinine was 1.8 mg/dL (normal range, 0.5 to 1.2 mg/dL), potassium was 4.8 mmol/L (normal range, 3.5 to 5.1 mmol/L), calcium was 7.7 mg/dL (normal range, 8.2 to 10.2 mg/dL), phosphorus was 4.6 mg/dL (normal range, 2.5 to 4.5 mg/dL), uric acid was 12.4 mg/dL (normal range, 2.5 to 8.5 mg/dL), and lactate dehydrogenase was 4420 IU/L (normal range, 200 to 400 IU/L), consistent with acute TLS		Acute TLS was diagnosed following laboratory findings.	Distal colonic stent was inserted through colonoscope to resolve the patients colonic stenosis but following metastases the patient was given 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy. Patient was also treated with IV hydration, diuresis, and allopurinol.	Following five cycles of FOLFOX chemotherapy, the patient showed hyperbilirubinemia and there was a progression of the primary tumor and metastatic hepatic lesions and peritoneal carcinomatosis that developed at this time. The patient ultimately died from septic shock.	Irregularly shaped ulceroinfiltrating mass in distal descending colon, irregular extracolonic nodules, liver metastases in the hepatic lobes.
Chao et al[95]	51-year-old Asian man had weight loss of 10 kg over a few months. Normal vital signs, painless abdominal mass over right upper quadrant. Urinalysis results displayed mild hematuria and amorphous urate crystals.	α-fetoprotein level was normal (5.25 μg/L, ref. <20 μg/L), whereas serum hepatitis B viral load was 5.53 × 106 IU/mL, hyperphosphatemia was 2.13 mmol/L; hyperuricemia was 892 μmol/L, and acute kidney injury was present	Hepatic B carrier since twenties without regular follow-ups.	Hepatocellular carcinoma was diagnosed	Transarterial chemoembolization for tumor reduction followed by a right hepatectomy. Allopurinol and aggressive hydration with urine alkalinization was administered. Patient was given a single 9-mg dose of rasburicase.	The patients acute kidney injury was unresponsive and he became orthopneic. Due to the rasburicase, the urine output increase after 2 days and his orthopnea symptoms ultimately subsided. Uric acid levels ultimately remained stable and	Hepatic mass in a cirrhotic liver that was 17 cm in diameter.

(Continues)

TABLE 4 (Continued)

Study	Clinical Manifestations	Laboratory Findings	History of Patient	Physician Diagnosis	Treatment	Outcome	Radiological Results
		(baseline creatinine 115-362 μmol/L. The acute kidney injury was unresponsive to allopurinol and aggressive hydration with urine alkalinization.				the patient was discharged.	

aforementioned numbers, and any symptomatic hypocalcemia.[1,36] If the patients are diagnosed with laboratory TLS, they are at high risk.[1,36]

More recently, laboratory data have revealed that addition of allopurinol, which blocks the conversion of hypoxanthine and xanthine to uric acid,[73-76] has led to a decline in hyperuricemia and hyperphosphatemia, becoming the principal laboratory abnormality.[41,77,78] For example, in a specific study with 102 patients who had intermediate- to high-grade non-Hodgkin lymphoma who had chemotherapy with allopurinol, 42% developed laboratory abnormalities and 6% developed the clinical definition of TLS.[10,46] Moreover, in a study where 100 adult patients with aggressive non-Hodgkin lymphoma received rasburicase for prophylaxis during initial chemotherapy treatment, the uric acid levels remained within the normal range throughout the chemotherapy treatment.[10,79] After more laboratory testing, it has been found that patients who are administered allopurinol are at high risk for xanthine nephropathy or xanthine stone formation because it is not catabolized, and this leads to uncertain effects.[10,75,80-82] However, rasburicase is preferred as it degrades uric acid into allantoin, which is more water soluble. It may not be preferred in patients with glucose-6-phosphate dehydrogenase deficiencies where uric acid breakdown can potentially lead to hemolytic anemia.[3,10,79] Vigorous hydration and lowering uric acid levels are also conventional treatments to mitigate the effects of TLS.[83] Other successful treatments include continuous peritoneal dialysis, hemodialysis, and continuous venovenous hemofiltration (CVVH). Of these, hemodialysis is most effective in reducing phosphorus levels. Dialysis is needed when phosphate levels are very severe and for renal complications.[71,84-86]

For prophylactic measures, urate oxidase is also an agent used for those who are in the high-risk chapter of TLS. This is due to the fact that urate oxidase is able to convert uric acid to allantoin, increasing solubility and thus excretion through urine.[87] This is preferred over allopurinol because there is not an increased chance of developing xanthine stones and there is no dose adjustment in acute renal failure and decreased adverse reactions.[87,88] Laboratory measures have shown that this treatment reduces serum uric acid levels and there is a lower incidence of renal failure that requires dialysis.[87] However, whether there should be single or multiple doses and if routine use is safe in children is still a question.[87]

Laboratory data have unveiled the incidence of TLS in children with advanced Burkitt lymphoma/leukemia in two multicenter trials. These 218 patients were treated with allopurinol as well along with intravenous hydration and urinary alkalinization. This study demonstrated that TLS (laboratory and/or clinical) ultimately developed in 16.1% of those affected with the cancers.[10,89]

5 | RADIOLOGICAL STUDIES OF TLS

Over the past several years, interventional radiology has become more prevalent in assessing appropriate treatment as it can replace or supplement traditional surgeries.[36] However, it has been shown that

TLS can result from interventional radiological procedures to treat oncologic diseases, showing that invasive radiology can be a factor to causing TLS as well.[90]

In terms of patients who have recently diagnosed cancer, imaging will help in the assessment of the extent and bulk of the cancer mass and allow a better understanding of the risk it will have for TLS. Renal ultrasonography is also potentially helpful in identifying masses that compress the kidneys, ureters, and bladder and to diagnose low urine output, a common result of TLS.[91]

6 | CONCLUSION

This review provides an updated understanding of TLS, accomplished by highlighting recent cases of the disease and how it manifests the body, associated risks, various criteria for grading, and different methods of treatment. To diagnose TLS unmistakably and promptly, clinicians must understand TLS physiology and its onset and progression. Case studies were provided as well, as seen in Table 4.[1,12,92-95]

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