Tumor Lysis Syndrome: A Comprehensive Review

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Abstract: *Tumor lysis syndrome (TLS) is a potentially life-threatening condition that can develop in oncologic and hematologic patients with a significant burden. This comprehensive review article provides an in-depth overview of TLS, including its epidemiology, etiology, pathogenesis, clinical presentation, diagnosis, prognosis, and treatment. The importance of early identification and prevention of TLS is emphasized. The article aims to enhance the understanding of TLS among clinicians and researchers in the field.*

Keywords: Tumor Lysis Syndrome, Oncology, Hematology, Review, Epidemiology, Etiology, Pathogenenesis, Clinical Presentation, Diagnosis, Treatment

1. Introduction

Tumor lysis syndrome (TLS) is a clinical disease resulting from a sequence of events that causes many malignant cells to die rapidly. It can arise spontaneously or after the initiation of chemotherapy. [1, 2] TLS is a metabolic and oncologic emergency that occurs frequently in clinical practice and has a high mortality rate, especially if the diagnosis is delayed and treatment is not administered promptly. This leads to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. All of these alterations have the potential to cause serious complications, including acute kidney injury, lethal cardiac arrhythmias, convulsions, and even mortality. [2–4]

The most critical component is quickly identifying people at risk for TLS to begin appropriate preventative and curative therapy. TLS usually occurs after the initiation of chemotherapy treatment. However, there are more reports of patients with high-grade hematology-oncology malignancies developing spontaneous TLS. [1, 2, 5] It occurs most frequently in patients with high-grade haematological malignancies, such as acute leukaemia and Burkitt's lymphoma, instead additionally can happen in patients with huge and rapidly developing solid tissue tumors, especially after chemotherapy. [2, 6, 7] It may arise spontaneously or as a consequence of antineoplastic treatment, such as conventional chemotherapy, corticosteroids, immunotherapy, radiotherapy, molecular-targeted therapy and chemoembolization. TLS patients may be saved by early diagnosis and treatment of renal and metabolic abnormalities. [1, 2, 4, 8]

Epidemiology

There are a number of intrinsic determinant factors that may raise the incidence of TLS. These risk factors include tumor burden, tumors with an extremely proliferating and respond sensitively to chemotherapy, and pre-existing renal disease or patient impairment. All of these variables can contribute to an increase in the likelihood of developing tumor lysis syndrome. TLS susceptibility is unrelated to race or gender. [2, 9] TLS, characterised by test abnormalities and clinical symptoms, is decreasing. Laboratory abnormalities were found in 42% of individuals, however only 6% had clinical TLS. The most prevalent malignancies linked with TLS include non-Hodgkin lymphoma (30%), solid tumors (20%), acute myeloid leukaemia (19%), and acute lymphocytic leukaemia (13%). Approximately 21 % of hospitalised patients died. [2, 9]

Etiology

TLS is most common in leukaemia patients with extremly high white blood cell (WBC) counts. It is observed in high-grade lymphomas, especially following the initiation of intensive chemotherapy. Other solid tumors that can lead to TLS include hepatoblastoma and neuroblastoma. Previously, initiation of chemotherapy, spontaneous TLS has been reported. [2, 10] The international experts has stratified tumors according to their likelihood of developing TLS[2] (table 1). TLS has been associated to biological immunomodulators, steroids, and monoclonal antibodies, however this is unusual. TLS is linked to hydroxyurea, thalidomide, paclitaxel, bortezomib, etoposide, fludarabine, and zoledronic acid. Rarely, TLS symptoms have been reported in general anesthesia patients. TLS may also be caused by pregnancy and excessively high temperatures. [2, 9, 11]

Table 1: Stratified risk tumors associated with tumor lysis syndrome[2]

High-risk tumors	Intermediate-Risk Tumors	Low-Risk Tumors
• Advanced Burkitt lymphoma • Advanced leukemia • Early-stage leukemia or Burkitt lymphoma with elevated lactate dehydrogenase • Acute lymphocytic leukemia with a white cell count of more than 100, 000/microliters, or if the increase of lactate dehydrogenase >2x ULN • Diffuse large B-cell lymphoma (DLBCL) and bulky disease with a baseline lactate dehydrogenase>2x ULN • Acute myeloid leukemia (AML) with a white cell count more than or equal to 10, 000/microliters	• AML with A white cell count between 25, 000 and 100, 000/microliters • Acute lymphocytic leukemia (ALL) with a white cell count of less than 100, 000/microL and LDH <2x ULN • DLBCL with a baseline increase in lactate dehydrogenase >2x ULN but the non-bulky disease • Early-stage leukemia and Burkitt lymphoma with a lactate dehydrogenase <2x ULN	• Solid cancers • Multiple myelomas • Indolent lymphomas • Chronic lymphocytic leukemia • Chronic myeloid leukemia • AML with a WBC count of less than 25, 000/microliters and a lactate dehydrogenase elevated <2x ULN

*ULN = upper limit of normal

Pathogenesis

Tumor lysis has a complex pathogenesis. Pathogenic pathways release more potassium, phosphorus, and nucleic acids during tumor cell lysis than homeostatic ones. TLS may develop spontaneously when cancer cells die without chemotherapy, embolization, or radiation therapy, or after cancer-specific treatment. [9, 12] TLS pathobiology and problems are caused by an intracellular chemical release. Kidneys excrete these chemicals. Excessive intracellular ion discharge might overwhelm the kidney's compensatory reaction, causing uric acid obstructive uropathy and acute kidney damage. [2, 13]

Nucleic acids (AMP, GMP) are metabolized into adenine and guanine, then hypoxanthine and xanthine, which xanthine oxidase converts into uric acid. [2, 14] Most mammals have the enzyme urate oxidase, which turns uric acid into allantoin, which the kidney can easily eliminate (5 to 10 times more soluble than uric acid). Humans and higher primates lack urate oxidase (OU), an enzyme needed for its catabolic process. Due to tumor cell turnover, uric acid production is high. The renal tubules crystallize this uric acid, causing obstructive uropathy, a lower glomerular filtration rate, and renal failure. [2, 9, 15] An blockage in the tubules causes a gradual rise in both the proximal and distal tubule pressure, which in turn leads to an increase in the peritubular capillary pressure and vascular resistance. Therefore, uric acid may induce kidney damage even via crystal-independent processes, such as changes in hemodynamics (renal vasoconstriction), and decreased autoregulation produced by a low nitric oxide level with vasoconstriction. Both of these alterations can occur as a result of uric acid. The removal of nitric oxide results in constriction of the blood vessels and ischemia of the kidneys. [1, 2, 13] Uric acid is another possible pro-inflammatory agent, and it may stimulate smooth muscle cells to produce cytokines such as tumor necrosis factor-alpha (TNF-alpha), mitogen-activated protein kinases (MAPK), monocyte chemotactic protein 1 (MCP1), and kappa-light-chain-enhancer of activated B cells (NFkB). These cytokines encourage the migration of white blood cells and contribute to the progression of kidney damage. [2, 9, 16]

The cell has 120–130 meq/L of potassium. Potassium enters the circulation as tumor cells lyse. Most of the potassium goes to the liver and skeletal muscle. [2, 4] The digestive system or kidneys remove the residue. Uric acid salts block the urinary tract, reducing potassium excretion. CKD or preceding AKI makes it more noticeable. Muscle fatigue, paralysis, arrhythmia, and death may result. [2, 9, 16] The nucleic acid has a phosphate group, and the disintegration of the cancerous cell will release a lot of phosphorus into the blood. Compared to normal cells, malignant cells contain four times more phosphate. Most phosphorus is removed via the kidneys. Chronic renal disease and acute kidney injury reduce the kidney's ability to handle phosphorus. Chronic renal disease is milder than acute kidney damage. Hyperphosphatemia is less common in spontaneous TLS because metabolically active tumor cells quickly absorb excess phosphate. This produces hypocalcemia by chelating calcium. Calcium and phosphorus salts may accumulate in the kidney and other soft tissues. When a calcium x phosphate product is more than 60 mg2/dL2, calcium phosphate precipitation in the renal tubules may cause acute kidney injury (AKI). Precipitation of calcium phosphate in the heart's conduction pathway may cause abnormalities and possibly fatal arrhythmias. Over the past several years, breakthroughs in hypouricemic therapy have rendered hyperphosphatemia the main mechanism of AKI in TLS. [2, 8, 9] Calcium binding to phosphate increases its toxicity. This illness kills more than hyperphosphatemia. Hypocalcemia may cause neuromuscular excitability, tetany, seizures, irregular heartbeats, and mortality. Hypocalcemia may persist after hyperphosphatemia is corrected, usually due to a vitamin D deficiency of 1.25. [2, 9]

Clinical presentation and diagnosis

The manifestation seen in patients diagnosed with TLS need to concentrate their attention on the fundamental reasons of tumor lysis. It is important to determine when the cancer first appeared while also paying attention to the existence of constitutional symptoms such as a loss of weight or anorexia. [2, 17] The development of respiratory symptoms such as dyspnea, orthopnea, and tachypnea might be an indication that an airway has been compressed due to the existence of a primary tumor. Symptoms related to the urinary tract, include dysuria, flank discomfort, and hematuria. Nausea, vomiting, seizures, tetanic spasms, and a change in mental state are some of the signs and symptoms that may be linked with hypocalcemia. Various clinical symptoms of TLS include syncopal attack, palpitation lethargy, pitting edoema, face edoema, abdominal distention, and various signs of fluid overload. [2, 9, 18]

The abnormalities in the electrolytes should be the primary focus of the physical examination since they are related with TLS. [8] Hypocalcemia symptoms include tetany, carpal spasm, pedal spasm, chvostek sign, and trousseau's sign. Wheezing, seizure, hyperuricemia, obstructive uropathy, weakness, lethargy, malaise, and other symptoms are associated with bronchospasm. nausea, vomiting, having a taste of metal on the tongue, irritability, broad pruritis, rales and ronchi from excessive volume, pericarditis, which is a complication of uremia, creates a muffled heart sound. [2, 16] Renal colic causes pruritis gangrene and joint pain. TLS symptoms might arise spontaneously or 72 hours after chemotherapy treatment begins. [2, 9]

The established diagnostic criteria that are utilised the most often, as well as Cairo and Bishop's suggested categorization. [19] TLS may be broken down into two categories: asymptomatic laboratory TLS (also known as LTLS), and clinical TLS (also known as CTLS). [2] A patient is considered to have LTLS if they exhibit at least two anomalies in their blood concentrations of uric acid, potassium, phosphorus, and calcium between three days before to the start of chemotherapy or seven days after the treatment has ended. CTLS is characterised as the existence of LTLS together with clinical signs of renal failure, seizures, or cardiac arrhythmias that are not a consequence of anticancer treatment (table 2). This combination of conditions is what distinguishes CTLS from LTLS. [7, 16, 20] The clinical symptoms of CTLS were graded on a scale from 0 to 5, with 0 indicating that there were no evidence of CTLS and 5 indicating that the patient had died as a result of

CTLS. CTLS was stratified using this grading method. In addition to this, it is essential to investigate and rule out any potential alternative causes of AKI. [2, 6, 7]

Table 2: Cairo–Bishop criteria for defining tumor lysis syndrome[19]

Cairo–Bishop Definition of Tumor Lysis Syndrome			
Laboratory TLS= modification of at least 2 parameters within 24 h	Uric acid $\geq$ 8 mg/dL Potassium $\geq$ 6 mg/dL Phosphate $\geq$ 4.5 mg/dL	Or 25% increase	within 3 to 7 days after chemotherapy initiation
		Or 25% decrease	
	Calcium $\leq$ 7 mg/dL		
Clinical TLS= laboratory TLS + 1 organ dysfunction or death	Renal dysfunction (creatinine > 1.5 X ULN) Cardiac involvement (arrhythmias) Neurological involvement (seizures, tetany) Death		

*ULN= Upper limit of normal

The parameters that Cairo and Bishop came up with had a few restrictions attached to them. The biggest drawback of utilizing these criteria to establish TLS is that it requires chemotherapy. Even without chemotherapy, spontaneous TLS formation is conceivable in clinical practice. The second limitation is creatinine levels over 1.5, which is the maximum for gender and age. CKD patients have high creatine levels even without AKI, therefore this is unusual. [2, 7, 9]

Treatment
Once it has been established, TLS requires a multidisciplinary approach as well as constant monitoring of many essential components. [9, 20]

1) Hydration
The first step in treating TLS is quickly increasing the patient's volume. Crystalloid solutions are used to do this, since they increase the volume of urine produced and, as a result, the amount of phosphate, potassium, and uric acid that are expelled. The fact that the renal functions should still be intact is a disadvantage of this approach. [2, 20, 21]The transfer of salt to the distal tubules also increases potassium output and decreases kalemia. Reducing the urine calcium phosphate product also prevents crystal formation. Intravenous hydration should start 48 hours before treatment and continue for 48 hours thereafter. To be hydrated, you may need to drink 3–3.5 liters/m2, or 4–5 liters daily. Adults should have a urine production of 100 mL/m2/hour, or 2.5 L/day. Urine production should exceed 4 mL/kg/hour for children. [2, 22, 23]

2) Electrolyte abnormalities management
Hyperkalemia may cause serious cardiac arrhythmias, hence potassium should be avoided in hydration fluid. Patients with potassium levels below 6 mmol/L should be continuously watched, and prompt action should be taken (intravenous infusions of calcium gluconate and glucose, as well as treatment with beta-adrenergic agonists). [9, 20]In the management of hypocalcemia, the administration of parenteral calcium chloride and calcium gluconate may be considered as viable therapeutic options. Regular calcium intake is not recommended due to its potential to promote calcium precipitating in soft tissues and exacerbate AKI. [2, 3, 9]TLS hypocalcemia results from hyperphosphatemia. Thus, calcium may worsen acute kidney damage by increasing calcium phosphate crystals in the renal system and soft tissues. Calcium is indicated in severe and symptomatic hypocalcemia, which may cause tetany, muscular fasciculation, bronchospasm, laryngospasm, ECG changes, and arrhythmia. Rather than normalizing calcemia, medication is used to relieve symptoms. [2, 7, 13]

Hyperphosphatemia management should address biological changes (e. g., phosphorus levels >1.62 mmol/l [>5 mg/dl]) that need medical intervention. A moderate asymptomatic hyperphosphatemia in chronic renal failure may be addressed by lowering dietary phosphate intake and using phosphate binders like aluminium hydroxide or aluminium carbonate (30 ml four times a day) to reduce stomach absorption. [2, 7, 14]Aluminum compounds should not be utilized long-term, especially in those with severe chronic renal illness, since aluminum is toxic. Acute renal damage might make hyperphosphatemia difficult to cure. Oral phosphate binders are less effective and harder to provide persons with this disease. Significant hyperphosphatemia is best treated with renal replacement therapy. [9, 10, 20]

3) Renal replacement therapy
RRT should be considered if the patient develops hypervolemia, the renal condition worsens despite treatment, or the electrolyte abnormalities persist. RRT treatment options include daily hemodialysis, continuous veno-venous hemofiltration, intermittent hemodialysis, and combination therapy. [1, 9]Hemodialysis can be used in a life-threatening scenario if the potassium and phosphorus levels are too high due to AKI-related TLS. Intracellular ions are continuously released in tumor lysis syndrome. Extracorporeal clearance may result in rebound hyperkalemia or hyperphosphatemia if intermittent hemodialysis is used. [3, 6, 20]Continuous renal replacement treatment removes solutes best. Dialysate or replacement fluid flow rates are high. Life-threatening hyperkalemia requires early hemodialysis. After successful TLS treatment, patients with severe acidosis, unresponsive volume overload, and protracted hyperkalemia should be offered renal replacement therapy. [1, 4, 20]

4) Hypouremic agents
Hyperuricemia predicts TLS and AKI, and uric acid levels affect AKI development. Thus, hyperuricemia must be monitored and treated. Hyperuricemia may be treated and prevented by drinking adequate water and utilizing a uric acid-lowering treatment. Rasburicase and allopurinol are the most often used antihyperuricemic drugs. [2, 24]

Allopurinol is a purine analogue and hypoxanthine isomer. These purines are related. Allopurinol is metabolized by

xanthine oxidase to produce oxypurinol, its active form. Oxypurinol inhibits xanthine oxidase competitively. Oxypurinol's 24-hour half-life and kidney elimination necessitate dosage modifications in renal failure. Oxypurinol lowers uric acid production from xanthine but does not influence existing production. Due to the combination of TLS and severe hyperuricemia, patients react poorly to treatment. Allopurinol increases blood levels of hypoxanthine and xanthine, which may precipitate in the renal tubules and cause acute kidney damage (AKI). [3, 7, 9]Allopurinol should be given prophylactically rather than in confirmed cases of TLS, especially in situations with rasburicase hypersensitivity or G6PD deficiency. Allopurinol is contraindicated in established TLS unless the patient has G6PD insufficiency. [2, 9, 20]Prophylactic treatments must begin at least 24 hours before the start of chemotherapy and must continue for at least seven days after treatment has ended. [17]Although uncommon, side effects of the medication can be severe and potentially fatal. These adverse reactions include Steven-Johnson syndrome, toxic epidermal necrolysis, acute toxic hepatitis, small vessel vasculitis, bone marrow aplasia, and DRESS syndrome, which is characterised by eosinophilia, rash, fever, lymphadenopathy, acute hepatitis, and acute interstitial nephritis. Prior research has demonstrated that the aforementioned adverse effects are idiosyncratic responses. [9, 16, 20]

Febuxostat is a new xanthine oxidase inhibitor. Because it does not cause the hypersensitivity responses that are associated with allopurinol and because it does not need the modification of the dosage based on the estimated glomerular filtration rate, it may serve as an alternative to allopurinol in some categories of patients. However, it is more expensive than allopurinol. [9, 25]

Rasburicase, recombinant urate oxidase, cures hyperuricemia in chemotherapy-treated leukemia, lymphoma, and solid tumor patients. Recombinant technology generated it from aspergillus. Recombinant urate oxidase was FDA-approved in 2009. The drug converts uric acid into allantoin, carbon dioxide, and hydrogen peroxide. [2, 9]Hydrogen peroxide, a potent oxidizer, may cause severe methemoglobinemia or hemolytic anemia in G6PD-deficient patients. G6PD deficiency should be tested before starting rasburicase medication. It can be muscle-injected. It may be regularly administered intravenously at 50–100 U/kg. Rasburicase has a quick impact (it decreases uric acid levels in under four hours), is relatively well tolerated, and has very few adverse effects. It interacts less than allopurinol. It may induce fever, headache, rash, nausea, vomiting, and hepatic cytolysis, hence pregnant women, nursing women, and G6PD deficient individuals should not take it. [2, 9]

2. Prognosis

The prognosis of TLS is inadequately documented, both pre-chemotherapy and post-treatment. Using recombinant urate oxidase has led to a significant decrease in the frequency of acute renal failure requiring hemodialysis. Better results have been achieved due to increased information about the biology of tumor lysis syndrome. The management regimen and therapy are both undergoing revisions due to improved knowledge on the pathophysiology of the illness. Because of this, there has been a dramatic reduction in the number of patients who have had unfavorable outcomes with TLS. [2, 26]

3. Conclusion

Tumor lysis syndrome is a potentially life-threatening condition that can occur in oncologic and hematologic patients with a significant burden. This article provides comprehensive reviews of TLS, including its epidemiology, etiology, pathogenesis, clinical presentation, diagnosis, treatment and prognosis. Early identification and prevention of TLS are crucial. Future research should focus on developing more effective strategies for the prevention and management of TLS.

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