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Tumor lysis syndrome: A review

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Abstract

Introduction: Tumor lysis syndrome is a clinical condition that can manifest suddenly or following the initiation of chemotherapy.

Purpose: To provide an overview of tumor lysis syndrome.

Methodology: This narrative review was conducted through a bibliographic search of reviews and research studies sourced from international databases. The exclusion criterion for the articles was any language other than English and Greek.

Results: Tumor lysis syndrome is a metabolic and oncological emergency commonly observed in clinical practice, reflecting the consequences of rapid tumor cell breakdown. It leads to disturbances in the patient's metabolic and electrolyte levels, causing hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. If not treated promptly, these conditions can pose a life-threatening risk to patients.

Conclusion: Tumor lysis syndrome is an emergency clinical condition linked to metabolic and electrolyte disturbances that, if not addressed quickly, can be fatal for patients.

Keywords: Tumor Lysis Syndrome; Management; Metabolic Disorders; Therapeutic management; Prognosis

1. Introduction

Tumor lysis syndrome (TLS) is a clinical condition that can occur spontaneously or following the initiation of chemotherapy. It is associated with various metabolic disturbances, including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, which can lead to end-organ damage. This syndrome is more prevalent in patients with solid tumors [1-2]. TLS refers to the pathological consequences of the rapid breakdown of tumor cells. In highly proliferative cancers, the cytotoxic effects of drugs, hormones, immunotherapy, and radiation can result in significant cell lysis, with electrolytes, nucleic acids, and proteins being released into the bloodstream, leading to metabolic disturbances [2].

TLS is a metabolic and oncological emergency frequently encountered in clinical practice, reflecting the pathological consequences of rapid tumor cell lysis [2-3]. Tumor cell lysis can be induced by chemotherapy or occur spontaneously. Although it is rarer, spontaneous TLS can lead to more severe clinical outcomes due to the lack of benefit from early treatment [4]. This condition is prevalent among both adult and pediatric oncology patients undergoing chemotherapy. Most symptoms observed in patients with TLS relate to the release of intracellular chemicals that disrupt the functions of target organs. This disruption can lead to massive cell lysis, acute kidney injury, arrhythmias, and sudden death [3-4]. Massive tumor cell death can occur in the context of successful cancer therapy or due to rapid tumor proliferation in

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uncontrolled disease [3-4]. The characteristic metabolic abnormalities of TLS include hyperkalemia, hyperphosphatemia, hypokalemia, and hyperuricemia. As laboratory tests become abnormal, a threshold is crossed beyond which clinical symptoms emerge [5-7].

The morbidities associated with the successful treatment of hematological malignancies become evident. Case series from the 1960s and 1970s described acute, severe hyperuricemia, hyperkalemia, hyperphosphatemia, and hypokalemia in children treated for acute lymphoblastic leukemia [5-7]. Similar metabolic disturbances have also been observed in adults with leukemia, whether under aggressive treatment or untreated. In some instances, the metabolic disturbances, collectively referred to as TLS, have led to severe clinical symptoms or required advanced interventions such as hemodialysis [6-8]. TLS typically develops after the initiation of chemotherapy, but there are cases of spontaneous development in high-grade hematologic-oncologic malignancies. Although rarer, spontaneous tumor lysis syndrome can result in more serious clinical outcomes due to the absence of benefits from early treatment [5-8]. Because this condition is highly lethal, it's essential to identify patients at high risk for developing tumor lysis syndrome and to initiate preventive therapy early. The complexity in managing TLS lies in diagnosing it early enough to initiate treatment before end-organ damage occurs. Predicting which patients are at risk is crucial and requires understanding the type of malignancy, its growth rate, response to treatment, and the type of anticancer therapy used [4-8]. With significant advancements in tumor biology knowledge, several new agents are now available for more targeted therapy. Moreover, established treatments have been continuously optimized. However, treatment-related complications continue to pose challenges in cancer care, despite major improvements in supportive care that have resulted in treatment-related mortality accounting for a high proportion of deaths in cancer patients [6-9]. Recognizing renal and metabolic issues linked to tumor lysis syndrome promptly and starting treatment can save lives [6-9].

2. Definition of Tumor Lysis Syndrome

According to Cairo and Bishop (2004) [4,10], TLS can be classified as either laboratory or clinical. The differential diagnosis is crucial for identifying patients who do not need specific therapeutic intervention versus those with life-threatening clinical abnormalities that require intervention, such as hemodialysis. In this classification, laboratory TLS is clinically silent and identified solely through laboratory testing, whereas clinical TLS is more complicated due to the clinical manifestations discussed below [11].

Laboratory TLS is marked by significant metabolic disorders that do not present clinical symptoms but still require treatment. A crucial condition for identifying laboratory TLS (LTLS) is the presence of two or more biochemical changes (uric acid ≥ 476 mmol/L, potassium ≥ 6.0 mmol/L, phosphorus ≥ 2.1 mmol/L in children and ≥ 1.45 mmol/L in adults, calcium ≤ 1.75 mmol/L, or a 25% increase from baseline in uric acid, with potassium and phosphorus showing greater than 25% decreases from baseline for calcium) occurring more than three days before or up to seven days after chemotherapy. In contrast, clinical TLS is characterized as a syndrome involving severe biochemical alterations and clinical symptoms that necessitate urgent intervention. Key indicators for identifying the clinical type of the syndrome are the laboratory indicators with one or more abnormalities, including an increase in creatinine (greater than 1.5 times the upper normal limit), cardiac arrhythmia, sudden death, and epileptic seizures [12-13]. It is necessary to note that the above definition contained some critical weaknesses. In particular, the specific indicators for laboratory TLS must be evaluated concerning adequate hydration and using a uric acid-lowering agent. On the other hand, more recent modifications of the definition of clinical TLS simplify the identification of the syndrome with the presence of at least one clinical criterion not attributable to the chemotherapeutic agent, while the parameter of reducing the aforementioned laboratory values (by 25%) from the baseline has been largely abandoned as not clinically significant in every case [14].

3. Epidemiology of Tumor Lysis Syndrome

The incidence of TLS is not well established. Several inherent risk factors may increase the likelihood of tumor lysis syndrome, including tumor weight, rapidly growing tumors, a high sensitivity to chemotherapy, and pre-existing renal disease or injury in the patient [13]. Race and gender do not appear to be associated with a predisposition to the syndrome. A study investigating the National Hospital Sample database found that the most common malignancies linked to TLS included non-Hodgkin lymphoma in 30%, solid tumors in 20%, acute myeloid leukemia in 19%, and acute lymphocytic leukemia in 13%. It is also noted that while TLS typically occurs early during neoplastic therapy, the incidence of spontaneous events has been reported to be significantly lower (around 1.08%). Additionally, TLS is less frequent in solid tumors but is more often associated with extensive tumors (greater than 10 cm on radiographic imaging) that are highly chemosensitive. The overall in-hospital mortality rate has been estimated to be approximately 21% [15-17]. TLS is most commonly associated with the initiation of cytotoxic chemotherapy. However, there are

reports of tumor lysis syndrome triggered by radiotherapy, including treatments involving thalidomide, dexamethasone, and newer chemotherapeutic agents such as rituximab and bortezomib [17].

4. Pathophysiology

The pathophysiology of TLS is complex. TLS occurs due to the massive release of intracellular ions, including potassium, phosphorus, and nucleic acids, that have been metabolized into uric acid. The primary organ responsible for eliminating these substances is the kidney. When the renal compensatory response is overwhelmed due to this massive release of intracellular ions, uric acid obstructive uropathy develops, which can then progress to acute kidney injury [18].

Hyperkalemia (elevated serum potassium levels), the primary laboratory indicator of TLS, can lead to severe dysfunction and weakness in skeletal muscles and the myocardium. Specifically, the cardiac effects of excessive potassium may result in ventricular tachyarrhythmias and sudden death. Uric acid, a byproduct of purine nucleotides, is produced during the breakdown of purines, first converting to hypoxanthine and xanthine through the action of the enzyme xanthine oxidase, and is ultimately degraded to uric acid. Due to the high cell turnover in cancer, large quantities of nucleic acids, purines, and uric acid are generated and released. Uric acid can obstruct the flow in the renal tubules (through crystallization), resulting in acute kidney injury and other forms of renal dysfunction (such as endothelial dysfunction, local ischemia, proinflammatory conditions, and impaired local renal repair mechanisms). Elevated serum phosphorus (resulting from cell death) may also contribute to acute kidney injury through similar pathways. The interaction of phosphorus with calcium (calcium phosphate) leads to pathological deposits in the kidneys and heart tissue, resulting in renal failure and arrhythmia respectively, while the decrease in unbound calcium levels leads to secondary neurotoxicity, manifested by epileptic seizures, psychiatric disorders, muscle tetany, and more [18-19].

5. Histopathology

Histopathological findings of TLS include the deposition of uric acid, calcium phosphate, and xanthine in the lamina propria of the distal renal tubules. Uric acid crystals can deposit in renal tubular epithelial cells and the medulla. Factors that favor crystal formation include low urine flow, low solubility, and high levels of solutes. Crystal deposition in the renal pelvis, calyces, and ureter can cause inflammation, obstructing urine flow. Long-term obstruction results in hydroureter, hydronephrosis, and subsequent acute renal failure [20].

6. History and Physical Examination

The history and physical examination of patients with TLS should concentrate on the primary causes of tumor lysis. The precise time of onset of the malignancy must be established, with particular attention given to the presence of symptoms such as weight loss or anorexia. Respiratory symptoms, including dyspnea, orthopnea, and tachypnea, may indicate airway compression caused by a primary tumor. The urinary system should be assessed for symptoms such as dysuria, pleuritic pain, and hematuria. Nausea, vomiting, seizures, tetanic spasms, and altered mental status suggest hypocalcemia. Additionally, clinical manifestations of tumor lysis syndrome encompass syncope, palpitations, lethargy, facial edema, abdominal distension, and signs of fluid overload [20-22].

7. Diagnostic findings

The diagnosis of TLS is based on criteria developed by Cairo and Bishop [3]. A significant drawback is that defining TLS according to these criteria necessitates the initiation of chemotherapy. Another limitation involves using creatinine levels exceeding 1.5 times the upper limit for age and sex. This is atypical, as a patient with chronic kidney disease may present elevated creatinine levels in the absence of acute illness. The Cairo and Bishop criteria also assess the severity of tumor lysis syndrome, ranging from grade 0, which is asymptomatic, to grade 4, which indicates death [20-23]. The laboratory diagnosis of tumor lysis syndrome requires at least 2 of the following criteria to be present within the same 24-hour period, from 3 days before to 7 days after the start of chemotherapy:

- Uric acid increase of 25% from baseline or greater than or equal to 8.0 mg/dL
- A potassium increase of 25% from baseline or greater than or equal to 6.0 mEq/L.
- Phosphorus should have a 25% increase from baseline or be greater than or equal to 4.5 mg/dL (greater than or equal to 6.5 mg/dL in children). Calcium should have a 25% decrease from baseline or be less than or equal to 7.0 mg/dL.

The clinical diagnosis of tumor lysis syndrome requires:

- Laboratory tumor lysis syndrome plus 1 or more of the following:
- Creatinine greater than 1.5 times the upper limit of normal of an age-adjusted reference range
- Seizures
- Cardiac arrhythmia or sudden death

Metabolic disorders linked to TLS include hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia. Blood urea nitrogen (BUN), creatinine, and lactate dehydrogenase levels also rise in TLS. These form the patient's metabolic panel and should be checked two to three times daily before and after initiating therapy. Elevated values indicate the onset of tumor lysis syndrome [20-22]. Urinalysis is also conducted because the presence and precipitation of uric acid salts can lead to obstructive uropathy. Hence, in treating tumor lysis syndrome, alkalinization of urine with sodium bicarbonate is considered the standard of care. Finally, thrombocytopenia, anemia, and leukocytosis are monitored [22-24].

8. Differential diagnosis

TLS should be distinguished from other clinical conditions that can cause:

- Hyperkalemia
- Hyperphosphatemia
- Hyperuricemia

The differential diagnosis of each electrolyte abnormality is as follows [22-24]:

8.1. Hyperkalemia

- Hypocalcemia
- Metabolic acidosis
- Congenital adrenal hyperplasia
- Digitalis toxicity
- Acute tubular necrosis
- Electrical burn
- Head trauma
- Rhabdomyolysis
- Thermal burns

8.2. Hyperphosphatemia

- Monoclonal gammopathy
- Waldenstrom macroglobulinemia
- Multiple myeloma
- Pseudohypoparathyroidism
- Rhabdomyolysis
- Vitamin D poisoning
- Oral saline laxative abuse
- Pseudo hyperphosphatemia

8.3. Hyperuricemia

- Hyperparathyroidism
- Hypothyroidism
- Nephrolithiasis
- Alcoholic ketoacidosis
- Diabetic ketoacidosis
- Gout
- Pseudogout
- Glycogen storage disease type 1
- Hemolytic anemia
- Hodgkin’s lymphoma

- Uric acid nephropathy

9. Therapeutic management

The treatment for TLS involves the excretion of substances associated with the syndrome, as well as specific drug therapies. This excretion is accomplished by increasing the glomerular filtration rate (GFR). Administering crystalloid fluids intravenously helps to increase the intravascular volume, which subsequently elevates the GFR, thereby aiding in the removal of substances. This initial treatment should be initiated within 48 hours before chemotherapy begins and continued for 48 hours following chemotherapy. Additionally, hydration of 3 to 5 liters per day is necessary to achieve urine production of 3 liters per day [24-25]. Specific drug therapies include administering bicarbonate, calcium, recombinant uric acid oxidase enzyme, allopurinol, febuxostat, and hemodialysis [24-26].

The administration of bicarbonate aims to alkalinize urine to solubilize uric acid. However, this alkalinization will also decrease ionized calcium, worsening the existing hypocalcemia from TLS. Therefore, it is recommended to continuously monitor calcium levels during bicarbonate administration [25-27].

Calcium chloride and gluconate are given intravenously to treat hypocalcemia, but this may affect the kidneys due to increased deposition of calcium phosphate crystals. For this reason, the patient may require dialysis [25-27].

Recombinant uric acid oxidase enzyme can be used to treat hyperuricemia associated with tumor lysis syndrome, having been approved by the FDA in 2009. This enzyme catalyzes the breakdown of uric acid into allantoin, carbon dioxide, and hydrogen peroxide. It can be administered either intravenously or intramuscularly [25-27].

Allopurinol is a structural isomer of hypoxanthine, with xanthine oxidase converting allopurinol to oxypurinol. Oxypurinol is an active metabolite primarily excreted by the kidneys. In patients with chronic kidney disease, the elimination of oxypurinol is impacted. Special care should be taken when administering allopurinol because it increases xanthine levels, potentially worsening obstructive uropathy associated with TLS. While allopurinol lowers uric acid levels in these patients, it cannot treat hyperuricemia. Allopurinol is a valuable tool in the therapeutic arsenal of health professionals to prevent the development of TLS. Lastly, particular attention should be given to the possible interaction of allopurinol with azathioprine and the use of immunosuppressive drugs in patients with solid organ transplants [25-27].

Febuxate is a new medication shown in the clinical trial (FLORENCE) to better control hyperuricemia associated with tumor lysis syndrome, exhibiting a good safety profile without affecting kidney function. Febuxate is a xanthine oxidase inhibitor that has demonstrated promise in managing patients with tumor lysis syndrome [27]. In instances where electrolyte levels (potassium and phosphorus) are elevated, early initiation of continuous renal replacement therapy is advised instead of intermittent therapy, as the latter may further worsen the condition. The goal of continuous renal replacement therapy is to remove elevated solutes that the body cannot eliminate due to chronic renal damage associated with the syndrome [25-27].

10. Prognosis

There is limited data in the literature regarding the prognosis of patients either before treatment begins or after it ends. With a better understanding of the disease's pathophysiology, improved outcomes have been achieved in patient management. Establishing a treatment protocol and its adaptation results in more effective treatment of the disease and a decrease in its associated consequences [27]. It is essential for the care plan to prioritize achieving an optimal quality of life, as is clear in other conditions, especially when the patient is admitted to the intensive care unit. This approach helps prevent additional complications in the ICU, such as post-intensive care syndrome and others. Ultimately, healthcare professionals can provide high-quality care by implementing appropriate strategies [28-33].

11. Conclusion

TLS is a critical clinical condition linked with metabolic and electrolyte disturbances that, if not addressed promptly, can be fatal for patients. The role of healthcare professionals in specialized hematology and oncology units is especially vital, as the early identification of high-risk patients and effective treatment through comprehensive care greatly helps minimize serious metabolic complications and enhance the success of anti-neoplastic therapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Gangireddy M, Shrimanker I, Nookala VK, Peroutka KA. Spontaneous tumor lysis syndrome in diffuse large B-cell lymphoma: early diagnosis and management. Cureus. 2019 May 16;11(5)

[2] Criscuolo M, Fianchi L, Dragonetti G, Pagano L. Tumor lysis syndrome: review of pathogenesis, risk factors and management of a medical emergency. Expert review of hematology. 2016 Feb 1;9(2):197-208

[3] Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. British journal of haematology. 2004 Oct;127(1):3-11

[4] Howard SC, Pui CH, Ribeiro RC. Tumor lysis syndrome. Renal Disease in Cancer Patients. 2014 Jan 1:39-64

[5] Ahmed Z, Barefah A, Wasi P, Jones G, Ramsay J. Tumour lysis syndrome in a patient with undifferentiated endometrial stromal sarcoma. Gynecologic Oncology Reports. 2019 May 1;28:41-3

[6] Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, Ortí G, Algarra L, Martínez J, Moscardó F, de la Rubia J. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica. 2008 Jan 1;93(1):67-74

[7] Jeha S. Tumor lysis syndrome. InSeminars in hematology 2001 Oct 1 (Vol. 38, pp. 4-8). WB Saunders

[8] Wolf G, Hegewisch-Becker S, Hossfeld DK, Stahl RA. Hyperuricemia and renal insufficiency associated with malignant disease: urate oxidase as an efficient therapy?. American Journal of Kidney Diseases. 1999 Nov 1;34(5):e20-1

[9] Bedrna J, Polcák J. Actuary ureter closure after irradiation with x-rays for chronic leukemias. Medizinische Klinik. 1929;25:1700-1\

[10] Mughal TI, Ejaz AA, Foringer JR, Coiffier B. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. Cancer treatment reviews. 2010 Apr 1;36(2):164-76

[11] Strauss PZ, Hamlin SK, Dang J. Tumor Lysis Syndrome: A Unique Solute Disturbance. The Nursing clinics of North America. 2017 Apr 7;52(2):309-20

[12] McGhee-Jez A, Batra V, Sunder T, Rizk S. Spontaneous tumor lysis syndrome as presenting sign of metastatic prostate cancer. Cureus. 2018 Dec 8;10(12)

[13] Wierda WG, Byrd JC, O'Brien S, Coutre S, Barr PM, Furman RR, Kipps TJ, Burger JA, Stevens DA, Sharman J, Ghia P. Tumour debulking and reduction in predicted risk of tumour lysis syndrome with single-agent ibrutinib in patients with chronic lymphocytic leukaemia. British Journal of Haematology. 2019 Jul;186(1):184-8

[14] Attina G, Tepedino R, Ruggiero A. Acute tumor lysis syndrome: a metabolic emergency in cancer patients. Biomedical and Pharmacology Journal. 2021 Sep 30;14(3):1721-9

[15] Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Advances in chronic kidney disease. 2014 Jan 1;21(1):18-26

[16] Chang YY, Chang CH, Ku WW, Gau JP, Yu YB. Tumor lysis syndrome as a risk factor for very early mortality in HIV-associated non-Hodgkin's lymphoma: a 10-year single-center experience. Journal of the Chinese Medical Association. 2020 Apr 1;83(4):371-6

[17] Ouzounakis P, Frantzana A, Iliadis C, Mihalache A, Alefragkis D, Kourkouta L. HIV infection and vaccinations. World Journal of Advanced Research and Reviews. 2023 Mar 30;17(3):101-6

[18] Williams SM, Killeen AA. Tumor lysis syndrome. Archives of pathology & laboratory medicine. 2019 Mar 1;143(3):386-93

[19] Belay Y, Yirdaw K, Enawgaw B. Tumor lysis syndrome in patients with hematological malignancies. Journal of oncology. 2017;2017(1):9684909

[20] Lupușoru G, Ailincăi I, Frăţilă G, Ungureanu O, Andronesi A, Lupușoru M, Banu M, Văcăroiu I, Dina C, Sinescu I. Tumor lysis syndrome: an endless challenge in onco-nephrology. Biomedicines. 2022 Apr 28;10(5):1012

[21] Von Amsberg G. Oncological emergencies in chemotherapy: Febrile neutropenia, tumor lysis syndrome, and extravasation. Der Urologe. 2018 May;57:552-7

[22] Strauss PZ, Hamlin SK, Dang J. Tumor Lysis Syndrome: A Unique Solute Disturbance. The Nursing clinics of North America. 2017 Apr 7;52(2):309-20

[23] McBride A, Trifilio S, Baxter N, Gregory TK, Howard SC. Managing tumor lysis syndrome in the era of novel cancer therapies. Journal of the advanced practitioner in oncology. 2017 Nov 1;8(7):705

[24] Jones DP, Mahmoud H, Chesney RW. Tumor lysis syndrome: pathogenesis and management. Pediatric Nephrology. 1995 Apr;9:206-12

[25] Gopakumar KG, Seetharam S, Km JK, Nair M, Rajeswari B, Cs G, Vr P, Thankamony P. Risk-based management strategy and outcomes of tumor lysis syndrome in children with leukemia/lymphoma: Analysis from a resource-limited setting. Pediatric Blood & Cancer. 2018 Dec;65(12):e27401

[26] Spina M, Nagy Z, Ribera JM, Federico M, Aurer I, Jordan K, Borsaru G, Pristupa AS, Bosi A, Grosicki S, Glushko NL. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. Annals of oncology. 2015 Oct 1;26(10):2155-61

[27] Chandra Mouli T, Samal S. Tumor Lysis Syndrome. InCritical Care Hematology 2024 Oct 26 (pp. 255-264). Singapore: Springer Nature Singapore

[28] Alefragkis D, Tousoulis D, Toutouzas K, Kyritsi E, Papageorgiou D, Polikandrioti M. Quality of life in patients with coronary heart disease before and six months after coronary artery bypass grafting (CABG). Nosileftiki. 2024 Jul 1;63(3)

[29] Giournta AM, Alikari V, Platis C, Oikonomopoulou G, Alefragkis D, Theofilou P. Assessing the quality of life and depression among patients with heart failure and heart attack. Health Psychology Report. 2020 Jun 1;8(3):211-8

[30] Alefragkis D. Post intensive care syndrome prevention and impact of COVID 19. Progress in Health Sciences. 2021 Jun 14;11:112-7

[31] Satolia K, Alefragkis D. Effect of daily sedation interruption and the patient's outcome who are under mechanical ventilation: A mini systematic review. International Journal of Medical Science And Diagnosis Research. 2020;4(12):1-4

[32] Alefragkis D, Kaba E, Mastorakis G, Narliotis G, Evgenikos K, Biagkis N, Papageorgiou D. Post COVID – 19 syndrome. Rostrum of Asclepius/Vima tou Asklipiou. 2023 Jan 2;22

[33] Papageorgiou D, Kosenai K, Gika E, Alefragkis D, Keskou D, Mandila C. Quantification of frailty syndrome in ICU patients with clinical frailty scale. Folia Medica. 2020 Dec 31;62(4):655-61