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Original Research Article

Tumor Lysis Syndrome in Adults with Hematologic Malignancies

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Abstract

Introduction: Tumor lysis syndrome (TLS) is a metabolic complication commonly seen in patients with hematologic malignancies, particularly high-grade non-Hodgkin lymphomas and acute leukemia. It is characterized by biochemical abnormalities that can lead to cardiac, neurological, and renal complications that can be fatal. The purpose of our study is to describe the epidemiology, laboratory profile and the outcome of TLS in order to identify patients at risk, and to implement appropriate prophylactic measures to prevent the clinical repercussions. ***Material and Methods:*** This work is a retrospective study of all patients who developed a laboratory TLS in hematologic malignancies according to the classification of Cairo and Bishop over a period of 3 years (from November 2019 to November 2022), and whose data were collected at the adult hematology unit of the Mohammed VI University Hospital of Tangiers. ***Results:*** The incidence of TLS among hematologic malignancies identified during this period was 3.7%. The underlying disease was acute leukemia in 10 patients (55.6%) and high-grade lymphoma in eight patients (44.4%). TLS was spontaneous in fifteen cases (83%) and chemotherapy-induced in three cases (17%). All our patients presented with hyperphosphatemia. 94% of cases had hyperuricemia, 44% of cases had hypocalcemia, while 6% of cases had hyperkalemia. Lactate dehydrogenase levels were elevated in all cases. Treatment consisted of hyperhydration and administration of hypouricemic agents in all cases. Three patients received hemodialysis. The outcome was favorable in 83% of cases and 17% of cases died during follow-up. ***Conclusion:*** TLS is a severe complication, most often seen in highly proliferative hematologic malignancies. The role of the laboratory remains paramount in the diagnosis of TLS and in the biological monitoring after the implementation of appropriate therapeutic measures.

Keywords: Tumour lysis syndrome, leukemia, lymphoma, metabolic abnormalities, outcome.

INTRODUCTION

Tumor lysis syndrome (TLS) is a hemato-oncological emergency caused by massive tumor cell lysis with the release of a significant amount of intracellular contents (potassium, phosphate and nucleic acids) into the systemic circulation, leading to hyperuricemia, hyperkalaemia and hyperphosphatemia associated with hypocalcemia [1]. These electrolyte disorders lead to life-threatening organ dysfunction, with acute renal failure, seizures and fatal cardiac arrhythmia [2]. It is most commonly seen after initiation of cytotoxic therapy in patients with highly proliferative hematologic malignancies (HMs), including high-grade non-Hodgkin lymphomas (NHLs), acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) [3]. However, TLS can occur spontaneously, and with tumors that are highly sensitive to cytotoxic therapy or have a high proliferative rate [4].

According to the Cairo and Bishop definition, TLS can be categorized as either laboratory TLS or clinical TLS [5]. Laboratory TLS is defined as having at least two isolated metabolic derangements within 3 days before or up to 7 days after the initiation of chemotherapy. On the other hand, clinical TLS is present when laboratory TLS is accompanied by one or more of the following abnormalities: creatinine level of at least 1.5 times the upper limit of normal, cardiac arrhythmia, seizures, or sudden death.

This syndrome is associated with significant morbidity as well as mortality. Identifying high-risk patients, monitoring electrolyte values, and taking

adequate prophylactic measures are necessary to prevent further complications.

The present study aimed to determine the frequency, epidemiology, laboratory profile and outcome of TLS in patients with HMs.

MATERIAL AND METHODS

Patients

This study aimed to describe the frequency, characteristics, management, and outcomes of TLS in patients with HMs admitted to the adult hematology unit of the Mohammed VI University Hospital of Tangier over a 3-year period. The study collected data on patient's age, gender, underlying hematologic malignancy, and whether TLS was spontaneous or therapy-induced. Laboratory tests including potassium, uric acid, phosphorus, calcium, lactate dehydrogenase (LDH), urea, and creatinine were also evaluated. TLS classification, management protocol, and outcome were also documented.

The classification of TLS used in this study was the Cairo and Bishop classification (Table I), which includes both clinical and laboratory criteria. The management protocol for TLS typically involves hydration, hypouricemic agents, electrolyte management, and, in severe cases, hemodialysis. The outcome measures included normalization of laboratory parameters, complications, and mortality.

Statistical Method

Age and biochemical parameters are presented as mean ± standard deviation (SD).

Frequency of TLS, gender, underlying haematological malignancy is presented as percentages.

Table I: Cairo-Bishop Definition for Laboratory and Clinical Tumor lysis syndrome

Laboratory TLS	Two or more of the following laboratory abnormalities within 3 days prior to and up to 7 days after initiation of cytotoxic therapy: Uric acid ≥ 476 µmol/L Potassium ≥ 6 mmol /L Phosphorus : ≥ 2,1 mmol/L for children, ≥ 1,45 mmol/l for adults Calcium ≤ 1,75 mmol/l OR 25% change from baseline in any of the above analytes
Clinical TLS	Laboratory TLS plus one of the following: Creatinine ≥ 1.5 times the upper limit of normal Cardiac arrhythmia Seizure Sudden death

RESULTS

The incidence of TLS among 480 medical records of HMs identified during this period was 3.7 %. The mean age of our patients was 46 ± 14.37 years (range 16 – 63) and 72 % of patients were male. Acute leukemia was the underlying disease in 55.6% of cases (n = 10), while high-grade non-Hodgkin lymphoma accounted for 44.4% of cases (n = 8) (Table II). TLS was spontaneous in 83 % of cases (n = 15) and chemotherapy-induced in 17 % of cases (n = 3). Hyperphosphatemia was observed in all patients, with a mean level of 2.04 ± 0.65 mmol/L, and hyperuricemia was noted in 94% of cases, with a mean level of 706.27 ± 223.23 µmol/L. Hypocalcaemia was present in 44% of patients, with a mean level of 1.63 ± 0.1 mmol/L, and hyperkalemia was only present in one patient (Table III). Clinical TLS was noted in 33 % of cases, all of whom presented with acute renal failure (ARF) with serum creatinine levels ranging from 22.6 to 127.45 mg/L. LDH levels were elevated in all cases with a mean of 1664 ± 1836 IU/L. Treatment consisted of hyperhydration and the administration of hypouricemic agents in all cases. Haemodialysis was performed in 17 % of cases (n = 3), the indication being established in collaboration with the nephrologists. The outcome was favorable in 83 % of cases, with an average time to laboratory remission between 3 and 20 days. However, 17 % of cases died, and death occurred within an average of 3 days.

Table II: Patient characteristics according to the underlying hematological malignancies

Pathology	**n**	**%**
Acute leukemia	10	55,6
Acute myeloid leukemia	7	
Acute lymphoblastic leukemia	3	
High-grade non-Hodgkin lymphoma	8	44,4
Diffuse large B-cell lymphoma	5	
Mantle cell lymphoma	2	
Burkitt lymphoma	1	

Table III: TLS laboratory abnormalities

	Patients (%)	Range values
Hyperphosphatemia (mmol/l)	18 (100 %)	[1,51 – 2,91]
Hyperuricemia (µmol/l)	17 (94 %)	[480 – 1351]
Hypocalcemia (mmol/l)	8 (44 %)	[1,46 – 1,70]
Hyperkalemia (mmol/l)	1 (6 %)	[6,3]
LDH ↑ (IU/L)	18 (100 %)	[311 – 6239]
Creatinine ↑ (mg/dL)	6 (33 %)	[22,6 – 127,45]

DISCUSSION

TLS is a well-known complication of highly proliferative HMs. Its incidence varies widely, and it is difficult to define due to the heterogeneous patient populations and lack of uniform diagnostic criteria [6]. However, TLS is most commonly seen in patients with high-grade NHL and acute leukemia, with less frequency in chronic leukemia and multiple myeloma [3]. According to a study by Wasim *et al.,* which involved 50 patients diagnosed with HMs, the incidence of TLS was 14%, 4%, and 2% for acute leukemia, NHL, and chronic leukemia, respectively [7]. It is important to note that this study represents only one cohort and may not reflect the incidence of TLS in all patient populations. Another multicentre study of 1255 patients found an overall incidence of TLS in 3.5% of cases, with a sex ratio (M/F) of 2.46 [8]. In the current study, we found a similar incidence of TLS, with 3.7% of cases affected. However, it is worth noting that the incidence of TLS may vary depending on the specific patient population and diagnostic criteria used.

Tumour lysis syndrome usually develops after initiation of chemotherapy, but there are also cases that occur spontaneously, where it develops without any cancer treatment [8]. High-grade and rapidly proliferating HMs such as Burkitt's lymphoma, acute myeloid leukemia, and diffuse large B-cell lymphoma are known to have a higher risk of developing TLS, both spontaneously and following treatment [9]. In our series, the incidence of spontaneous TLS was 83%, which is exceptionally high. This could be due to the high-grade and rapidly proliferating nature of the tumors studied, leading to a large tumor burden and a higher likelihood of spontaneous. As a result, it is essential to monitor patients with these malignancies closely, as they may be at higher risk of developing TLS, both spontaneously and after initiation of therapy.

TLS is a medical emergency that occurs due to the rapid breakdown of malignant cells and the release of intracellular substances into the bloodstream. As a result, there is a surge in the levels of potassium, phosphorus, and uric acid, which can cause serious metabolic derangements and life-threatening complications [10]. Hyperkalemia is a major concern in TLS because it can cause cardiac arrhythmias, cardiac arrest, and sudden death [11]. The high levels of potassium in the bloodstream can affect the electrical activity of the heart and impair its ability to pump blood effectively. Hyperphosphatemia is another important metabolic disturbance in TLS, as it can lead to the precipitation of calcium phosphate crystals in the tissues, resulting in hypocalcemia [4]. The low levels of calcium can cause muscle cramps, tetany, seizures, and cardiac arrhythmias [10]. Therefore, managing phosphorus levels is crucial to prevent hypocalcemia and its associated complications. Hyperuricemia is also a common finding in TLS, and it can cause urate crystal formation and deposition in the renal tubules, leading to acute kidney injury (AKI) and renal failure [4]. In our series, the most common metabolic disturbances found were hyperphosphatemia and hyperuricemia.

Clinical tumour lysis syndrome is defined as a laboratory TLS with the association of at least one of the following criteria: elevated creatinine (at least 1.5 times the upper limit of normal) not attributable to another cause, cardiac arrhythmia or sudden death, and seizures. A retrospective study of hospitalised patients with tumour lysis syndrome between 2010 and 2013 found a significant proportion (58%) of patients with acute renal failure but a very low rate of seizures was reported (1%) [12]. In other studies, acute renal failure was almost constant with proportions of 81.8% and 81% respectively [8, 13]. The finding that clinical TLS was present in 33% of cases in this series highlights the importance of monitoring and managing TLS in patients with cancer who are at risk for this complication.

The risk of TLS can be further stratified based on specific clinical and laboratory parameters. For example, in high-grade NHL, the risk is higher in patients with elevated LDH levels. In ALL and AML, high-risk features include a high white blood cell count (usually defined as ≥100 x 10^3/µl) and LDH levels of 2 times the upper limit of normal or more [14]. All patients in our study had high LDH levels, suggests that TLS should be routinely expected and prevented in patients with high doubling time and high tumor mass.

All patients in our study received hyperhydration and hypouricemic treatments to prevent and manage TLS. Maintaining high urine output with adequate hydration is crucial to prevent uric acid and calcium phosphate crystal precipitation in the renal tubules [15]. Allopurinol is the drug of choice for prophylaxis in patients at low or intermediate risk of developing TLS, while rasburicase may be more

effective in patients with hyperuricemia and urate crystals already formed [16]. The use of diuretics has been suggested to improve urine output and decrease the risk of crystal precipitation, but none of our patients received them. Continuous cardiac monitoring and electrolyte assays are necessary for patients with hyperkalemia or hypocalcemia due to the risk of fatal arrhythmias [3]. Hemodialysis is indicated when patients do not respond to therapeutic measures and to correct electrolyte disorders, hyperuricemia, and renal failure associated with TLS [10]. The prognosis of TLS is difficult to determine, but poor prognostic factors include AKI, nephrocalcinosis, and life-threatening cardiac rhythm disturbances [2]. In this series, 83% of the cases had a favorable outcome, while mortality occurred in three patients following AKI.

CONCLUSION

Recognition of the features of Tumor Lysis Syndrome, including laboratory abnormalities such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, is critical for prompt implementation of appropriate prophylactic measures, which typically involve aggressive hydration, urate-lowering therapy, and electrolyte management. With early recognition and appropriate management, the prognosis for Tumor Lysis Syndrome has improved in recent years.

REFERENCES

1. Zafrani, L., Canet, E., & Darmon, M. (2019). Understanding tumor lysis syndrome. *Intensive Care Medicine*, *45*, 1608-1611.
2. Eng, S., Lee, C. S., Ahn, S., & Sharma, A. (2020). A retrospective analysis of tumor lysis syndrome management in a quaternary care hospital. *Journal of Oncology Pharmacy Practice*, *26*(2), 338-344.
3. Williams, S. M., & Killeen, A. A. (2019). Tumor lysis syndrome. *Archives of pathology & laboratory medicine*, *143*(3), 386-393.
4. Rahmani, B., Patel, S., Seyam, O., Gandhi, J., Reid, I., Smith, N., & Khan, S. A. (2019). Current understanding of tumor lysis syndrome. *Hematological oncology*, *37*(5), 537-547.
5. Cairo, M. S., & Bishop, M. (2004). Tumour lysis syndrome: new therapeutic strategies and classification. *British journal of haematology*, *127*(1), 3-11.
6. Lupușoru, G., Ailincăi, I., Frățilă, G., Ungureanu, O., Andronesi, A., Lupușoru, M., ... & Sinescu, I. (2022). Tumor lysis syndrome: an endless challenge in onco-nephrology. *Biomedicines*, *10*(5), 1012.
7. Wasim, F., Khaskheli, A. M., Siddiqui, A. A., Tariq, O., & Ansari, M.A. (2012). Tumour lysis syndrome in haematological malignancies. *Journal of the Liaquat University of Medical and Health Sciences*, *11*(2), 84–89.
8. Akhrouf, S., Talbi, A., Belhadri, F., Moussaoui, H., & Hamladji, R. M. (2015). Evaluation of the frequency and management of the Lysis Syndrome in hematology. *Algerian revue of hematology*, *10*, 71-74.
9. Gangireddy, M., Shrimanker, I., Nookala, V. K., & Peroutka, K. A. (2019). Spontaneous Tumor Lysis Syndrome in Diffuse Large B-cell Lymphoma: Early Diagnosis and Management. *Cureus*, *11*(5), e4679.
10. Belay, Y., Yirdaw, K., & Enawgaw, B. (2017). Tumor lysis syndrome in patients with hematological malignancies. *Journal of Oncology*, *968*(4), 90-99.
11. Howard, S. C., Jones, D. P., & Pui, C. H. (2011). The tumor lysis syndrome. *N Engl J Med*, *364*(19), 1844-54.
12. Durani, U., Shah, N. D., & Go, R. S. (2017). In-Hospital Outcomes of Tumor Lysis Syndrome: A Population-Based Study Using the National Inpatient Sample. *Oncologist. 22*(12), 1506-1509
13. Kaci, Z., Belhani, M., & Boudjerra, N. (2015). Metabolic disorders and tumor lysis syndrome during acute leukemia: experience of the hematology department of Béni Messous University hospital. *Algerian revue of hematology*, *10*, 66 -69.
14. Cairo, M. S., Coiffier, B., Reiter, A., Younes, A., & TLS Expert Panel. (2010). 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. *British journal of haematology*, *149*(4), 578-586.
15. Abu-Alfa, A. K., & Younes, A. (2010). Tumor lysis syndrome and acute kidney injury: evaluation, prevention, and management. *American journal of kidney diseases*, *55*(5), S1-S13.
16. Jones, G. L., Will, A., Jackson, G. H., Webb, N. J., Rule, S., & British Committee for Standards in Haematology. (2015). Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *British journal of haematology*, *169*(5), 661-671.