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TUMOR LYSIS SYNDROME: ETIOLOGIES, PATIENT PROFILE, MANAGEMENT AND THERAPY

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Abstract: Introduction: Tumor lysis syndrome (TLS) is an oncological emergency caused by the massive disintegration of tumor cells and the abrupt release of intracellular contents, such as potassium, phosphate and nucleic acid, into the bloodstream. **Objectives:** To present the main concepts of SLT, focusing on its etiologies, patient profile, management and therapy**. Methodology:** A narrative review of the literature was carried out based on 24 articles, which varied between 2016 and 2023. **Results:** TLS is an underreported oncological emergency that occurs after initiation of treatment for hematological malignancies. As etiologies, we can mainly mention chemotherapy. Its main risk factors include tumor characteristics such as metastatic disease and high proliferation rate. The pathophysiology directly correlates with the clinical picture, as it results from the release of potassium, phosphorus and nucleic acid ions into the bloodstream. The main manifestation of the disease may be acute kidney injury (AKI), caused by hyperuricemia or precipitation of calcium phosphate. For diagnosis and risk stratification of the syndrome, the Cairo and Bishop criteria are used, consisting of laboratory evaluation and the patient's clinical picture. The management of TLS must begin with the appropriate investigation of the disease by prior identification of the patient's profile and risk factors, looking for signs and symptoms such as weight loss, fever, bleeding and lymph node disease. The main approach is isotonic hydration. **Conclusion:** TLS is an oncological emergency and can be triggered by chemotherapy and spontaneous cell lysis. The clinical picture of the pathology presents with ARF, cardiac arrhythmias, nausea, vomiting, lethargy and sudden death. Management must be individualized and involves isotonic hydration and urate lowering. In case of refractory AKI, oral phosphate binders, diuretics and emergency hemodialysis can be adopted.

Keywords: Tumor Lysis Syndrome; Therapy; Etiology; Clinical Management

INTRODUCTION

Tumor lysis syndrome (TLS) is an oncological emergency caused by the massive disintegration of tumor cells and abrupt release of intracellular contents, such as potassium, phosphate and nucleic acid into the bloodstream (1). This situation can generate a significant hydroelectrolyte imbalance characterized by hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcemia, favoring the emergence of arrhythmias, acute kidney injury, seizures and even multiple organ failure (1,2).

Hematological malignancies have a higher probability of developing TLS compared to solid tumors (3). Solid neoplasms and slow-growing hematological malignancies are considered less prone to TLS due to their lower proliferation rate, smaller tumor volume and relatively reduced resistance to therapy (4). TLS is typically linked to chemotherapy, although it can also occur after radiation treatment and therapies with monoclonal antibodies such as anti-CD20 (4,5).

Due to its variable incidence in different types of cancer and the diversity of therapeutic regimens, the understanding of the epidemiology of TLS is not yet complete (3). In a study carried out by the SOLCA-Cuenca Cancer Institute, TLS most frequently affected males in 57.7% of cases, with acute lymphoblastic leukemia (ALL) being the most common diagnosis, present in 61.5%. of patients. Then there was the occurrence of chronic myeloid leukemia (CML) and retinoblastoma, each representing 7.6% of cases (6). The main risk factors include especially acute myeloid leukemia (AML), ALL and Burkitt's lymphoma, all of which are

considered high risk for TLS (5).

Symptoms depend on metabolic disorders, including lethargy, nausea, vomiting, diarrhea, myalgia, muscle cramps, paresthesia, spasmodic muscle contractions, convulsions, cardiac arrhythmias, syncope and, in the absence of effective therapy, can lead to death (2). These symptoms may be preventable with aggressive hydration, diuretics, and hypouricemic medications. Electrolyte correction, cardiac monitoring and renal parameters are crucial treatment strategies (7,8).

Given this scenario, as TLS is a complication that can lead to death, with a risk of predictable serious complications that can be avoided with a preventive plan, knowledge by the medical team of the manifestations, metabolic consequences and etiology of TLS is essential for prevention, early recognition of complications, adequate treatment and a good prognosis (3,7,8). This review aims to present the main concepts of tumor lysis syndrome, focusing on its etiologies, patient profile, management and therapy.

GOALS

This review aims to present the main concepts of tumor lysis syndrome, focusing on its etiologies, patient profile, management and therapy.

METHODOLOGY

A narrative review of the literature was carried out based on 24 articles, which varied between 2016 and 2023, in the months of March, April and May 2024. The articles covered the English, Spanish and Portuguese languages and were taken from the Pubmed databases and Lilacs. The descriptors used were "Tumor Lysis Syndrome", "Therapeutics", "Etiology", "Clinical Management".

RESULTS

TLS is an underreported oncological emergency that occurs after the start of treatment for hematological malignancies, being a differential diagnosis for acute kidney injury (AKI) and electrolyte abnormalities (9). The etiologies include chemotherapy and, to a lesser extent, spontaneous lysis. Therefore, its main risk factors include tumor characteristics such as metastatic disease and high proliferation rate, in addition to patient characteristics such as dehydration, infections, high levels of uric acid and lactate dehydrogenase enzyme (LDH) and previous exposure to nephrotoxic agents (10).

The pathophysiology directly correlates with the clinical picture, as it results from the release of potassium, phosphorus and nucleic acid ions into the bloodstream. From the release of these cellular components, hyperphosphatemia forms calcium phosphate, causing hypocalcemia. Therefore, the main manifestation of the disease may be acute kidney injury (AKI), caused by hyperuricemia or precipitation of calcium phosphate. Hyperkalemia is related to cardiac arrhythmias and sudden death (11, 12). Likewise, the release of inflammatory cytokines occurs, inducing systemic inflammatory response syndrome, sepsis and organ failure (13). Anemia, neutropenia and thrombocytopenia are also common (14).

Clinical manifestations can be nonspecific, such as nausea, vomiting and lethargy and generally occur 3 days after the start of chemotherapy therapy. The profile of individuals affected by SLT varies according to the characteristics of each neoplasm, the patient's condition and comorbidities and the type of treatment used (15). As examples, it may be associated with Burkitt's lymphoma, acute lymphoblastic leukemia, rapidly proliferating lymphomas and chronic leukemias (16). Individuals with tumors with

a high mitotic rate, previous nephropathy and high sensitivity to defined therapy are more prone to TLS. Therefore, an individualized approach is necessary for each patient (1).

TLS presents high mortality, especially in solid tumors (18,19). For diagnosis and risk stratification of the syndrome, the Cairo and Bishop criteria are used, consisting of laboratory evaluation and the patient's clinical picture. Laboratory criteria encompass two of the following: hyperphosphatemia, hyperkalemia, hypocalcemia, and hyperuricemia. The clinical picture must have the presence of one of the criteria of acute kidney injury, convulsive crisis, cardiac arrhythmia or sudden death (20,21).

The management of tumor lysis syndrome must begin with the appropriate investigation of the disease by prior identification of the patient's profile and risk factors, looking for signs and symptoms such as weight loss, fever, bleeding and lymph node disease (5). Next, laboratory electrolyte collection takes place (2). For this reason, the main approach is isotonic hydration, which also serves as prophylaxis for these emergency complications of the disease (5).

New laboratory tests must be ordered every 4-6 hours to reevaluate critical conditions (5,2,22). Given the risk of cardiovascular arrhythmias, hyperkalemia needs to be treated as a priority. The initial approach is to perform an electrocardiogram to analyze specific changes in this electrolyte imbalance. Options for this management include nebulized beta-2 agonists, the combination of glucose and insulin and calcium gluconate, which can also be useful in mixed disorders involving hypocalcemia, for example (22).

Hypocalcemia frequently occurs in conjunction with hyperphosphatemia, which must be corrected quickly due to the possible complication of acute kidney injury (1). Initial management is through hydration itself, however, if there is little or no response, there is the possibility of using oral phosphate binders to inhibit intestinal absorption of the electrolyte (5). If hyperphosphatemia is severe, the patient becomes eligible for emergency hemodialysis (23).

Among the pillars of treatment, in addition to hydration, it is necessary to maintain adequate urine production for several days after completing therapy, together with urate-lowering agents (allopurinol or rasburicase), (18,22). Allopurinol, due to its potential to competitively inhibit the enzyme xanthine oxidase, is used to prevent the precipitation of uric acid crystals in the renal tubules (2,24,21). It is generally indicated for patients with low to intermediate risk (2,8). On the other hand, uricase (urate oxidase) can be used, an enzyme that catalyzes the oxidation of uric acid and allantoin, which is more soluble and less toxic than uric acid (22). Today, recombinant rasburicase is used, a potent and fast-acting uricolytic agent, which currently has a lower risk of hypersensitivity (2,22). As it is a high-cost drug, it is indicated for high-risk patients or those who have uric acid levels greater than 8 mg/ml at the beginning of their course (2,24,8). The use of sodium bicarbonate is not recommended, as there is no evidence to justify its use (22). Furthermore, urine alkalinization must be avoided and, if dialysis is necessary, it is preferred before chemotherapy, when possible (2,24). If diuresis is not adequate, diuretics (furosemide) can be used, unless you have obstructive uropathy or hypovolemia (22).

Hemodialysis must not be postponed in the presence of hypervolemia secondary to TLS, hydroelectrolyte changes refractory to clinical measures and in the presence of significant acute kidney injury (2,24,18). Conventional hemodialysis results in better correction of hyperphosphatemia and continuous hemofiltration is more useful in critically ill patients with hemodynamic changes (18,22).

In general, peritoneal dialysis is less effective in lowering uric acid than hemodialysis and is not useful in eliminating phosphates (22). During the dialysis period, treatment of the underlying disease must not be suspended, but it is important to take into consideration, the nephrotoxicity of the medications used (22).

CONCLUSION

TLS is an oncological emergency and can be triggered by chemotherapy and spontaneous cell lysis. Therefore, it affects patients with malignancies with a high metastatic rate and significant risk factors, such as previous nephropathy. The clinical picture of the pathology presents with ARF, cardiac arrhythmias, nausea, vomiting, lethargy and sudden death. For diagnosis and risk stratification, the Cairo and Bishop criteria are used. Therefore, once the profile of the syndrome has been identified, laboratory electrolyte collection and an electrocardiogram must be performed. Management must be individualized and involves isotonic hydration and urate lowering. Furthermore, in case of refractory AKI, oral phosphate binders, diuretics and emergency hemodialysis can be adopted.

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