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Case Report

Spontaneous Tumor Lysis Syndrome

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Keywords
Acute renal failure · Hyperkalemia · Hyperuricemia · Oncological emergency · Spontaneous tumor lysis syndrome

Abstract
Tumor lysis syndrome (TLS) is a hemato-oncological emergency characterized by metabolic and electrolyte imbalances which are associated with disintegrating tumor cells. The syndrome is frequently observed when starting cytotoxic treatment of hematological malignancies, while the incidence of spontaneous tumor lysis prior to the start of tumor therapy is rare. Here, we present a case of spontaneous TLS in a male patient who was referred with unspecific symptoms and suspected metastatic malignancy. He developed acute renal failure before the diagnosis of a high-grade B-cell lymphoma (double hit lymphoma) and start of therapy. Although the course of TLS would have required intensive care, the patient rejected such treatment for personal reasons and died soon after the discontinuation of therapy. The case emphasizes the life-saving relevance of early detection and appropriate treatment of TLS. It also demonstrates the importance of actively screening for TLS, primarily in patients with malignant diseases and high tumor load, even if they are not receiving cytotoxic therapy.

Introduction

Tumor lysis syndrome (TLS) is a hemato-oncological emergency [1–4]. It results from rapid lysis of malignant cells, which leads to the immediate release of various intracellular cell components (uric acid, potassium, and phosphate) [5]. The syndrome is typically associated with the development of hyperuricemia, hyperkalemia, and hyperphosphatemia with subsequent hypokalemia. These electrolyte imbalances cause life-threatening organ

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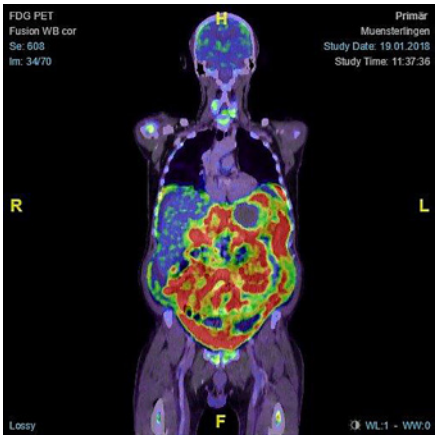

Fig. 1. Image showing abdominal tumor mass prior to initating therapy (FDG-PET-CT). Figure reprinted with kind permission of Thomas Kelly, Senior Physician Nuclear Medicine, Cantonal Hospital Münsterlingen, Münsterlingen, Switzerland.

dysfunction, with acute renal failure and fatal cardiac arrhythmia among the most severe manifestations.

TLS generally occurs at the beginning of chemotherapy or immunotherapy for specific tumor entities [6]. Significant tumor-associated factors include a high tumor load, a high proliferation rate, and the chemosensitivity of the underlying disease [2, 7–9], along with clinical and individual risk factors, such as advanced age, pre-existing renal insufficiency or hyperuricemia, and reduced volume status [6]. In rare cases, TLS can also occur spontaneously [10–18]. The condition must be actively tracked in regular laboratory checks for detection.

Case Report

Medical History

A 75-year-old patient suffering from suspected metastatic malignant disease with unknown primary tumor was referred to our oncological outpatient clinic for further investigation and the initiation of an appropriate therapy. During the initial consultation, the patient described a cumulative 4-kg loss of body weight within 3 weeks with a simultaneous increase in abdominal circumference, loss of appetite, and heartburn as well as pronounced night sweats and thirst. He also reported a rapid decline of physical fitness with progressive dyspnea.

The computed tomography (CT) examination of the chest and abdomen (January 19, 2018), performed previously on an outpatient basis, had revealed the clinical picture of malignant metastatic disease with 4-quadrant ascites, peritoneal depositions, and an infiltrated omentum (PET-CT image) (Fig. 1, 2). The imaging procedures had not been able to clearly detect a primary tumor.

In the first consultation, the patient emphasized his clear preference for alternative healing methods. He strongly opposed against intensive care therapy.

In the initial examination (January 15), the patient presented in good general condition. We noted a distended abdomen with reduced bowel sounds and pain in the epigastric and right lower abdominal area.

The laboratory analysis (January 15) showed significantly elevated inflammatory parameters (C-reactive protein 66 mg/L, leukocytosis 12.7 g/L with neutrophilia) as well as an elevated creatinine level of 118 µmol/L, a lactate dehydrogenase (LDH) value 10 times above

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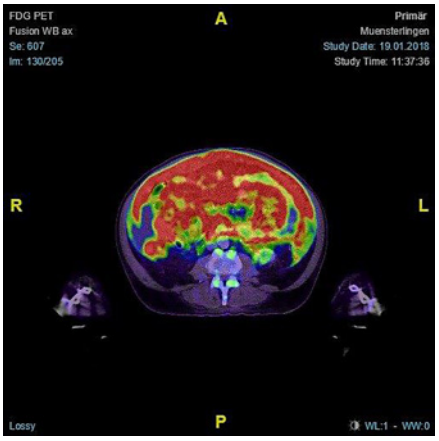

Fig. 2. Image showing abdominal tumor mass prior to initating therapy (FDG-PET-CT). Figure reprinted with kind permission of Thomas Kelly, Senior Physician Nuclear Medicine, Cantonal Hospital Münsterlingen, Münsterlingen, Switzerland.

the reference value (4,758 U/L), and a uric acid value 2 times above the reference value (738 µmol/L), with all other electrolytes in the normal range.

The PET-CT examination revealed pronounced FDG depositions in the peritoneum, mesentery, and pleura with a distribution pattern comparable to primary effusion lymphoma. A CT-guided biopsy of the pleural mass (January 22) showed a high-grade B-cell lymphoma (double hit lymphoma) with a high proliferation rate Ki-67 of approximately 90%.

Seven days after the first visit in our clinic, hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, as well as a further increase of creatinine (246 mmol/L), LDH, and urea occurred, in parallel to the worsening clinical condition. Accordingly, the patient met the criteria for spontaneous clinical TLS.

After repeated discussions, the patient agreed to enter the hospital. We started intravenous hydration and rasburicase and we initiated a pre-phase chemotherapy with prednisone (100 mg/day p.o.) and vincristine (2 mg i.v.). The patient finally agreed to a transfer to the intensive care unit for hemodialysis.

While the patient's kidney function recovered (creatinine 134 mmol/L) and his hyperuricemia and hyperkalemia leveled out, his overall condition deteriorated and the patient wished to go to the palliative care unit where he died a few hours later. The subsequent autopsy did not show any macroscopically or microscopically identifiable infiltrates of the previously diagnosed high-grade B-cell lymphoma.

Discussion

This is the case of 75-year-old patient with spontaneous TLS due to high-grade B-cell lymphoma with a high proliferation rate and a large tumor mass in the abdomen. TLS occurred before the initiation of chemotherapy. Being uncertain regarding therapy from the beginning, the patient finally decided to stop treatment and died in the palliative care unit. However, this leaves the question of how to improve the early detection of a TLS risk constellation to avoid TLS-related deaths.

How Is TLS Defined?

The classification and definition of TLS dates back to 2004 and is based on the Cairo-Bishop criteria, which distinguish between laboratory TLS and clinical TLS [6, 19]. Laboratory TLS is present if at least 2 of the laboratory values for uric acid, potassium, or phosphate are

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Table 1. Cairo-Bishop definition of laboratory tumor lysis syndrome (TLS) [2–4, 22]

Laboratory value	Serum concentration
Uric acid	≥476 μmol/L or >25% increase from baseline
Potassium	≥6 mmol/L or >25% increase from baseline
Phosphate	≥1.45 mmol/L or >25% increase from baseline
Calcium	≤1.75 mmol/L or >25% decrease from baseline

≥2 laboratory value changes or >25% increase from baseline 3 days before or 7 days after cytotoxic therapy.

Table 2. Cairo-Bishop definition of clinical tumor lysis syndrome (TLS) [2–4, 22]

Organ dysfunction	Stage		
	1–3	4	5
Serum creatinine	1: 1.5× ULN 2: >1.5–3.0× ULN 3: >3.0× ULN	>3.0–6.0× ULN	Death
Cardiac arrhythmias	1: No intervention required 2: Asymptomatic, drug intervention required 3: Symptomatic, cannot be controlled with medication, controlled with defibrillator	Life-threatening, arrhythmias with signs of cardiac decompensation	
Seizures	1: None 2: Short generalized seizure, seizures controlled by medication, focal seizures 3: Seizures with impaired consciousness, generalized seizures	Seizures of any kind that are prolonged, repetitive	

Clinical TLS is defined as laboratory TLS plus ≥1 organ dysfunction. Stage 4 is associated with an immediate danger to life. Stage 5 indicates death.

pathologically elevated or if a 25% increase from baseline can be documented within 3 days before or 7 days after the initiation of chemotherapy. The reverse applies to the serum values for calcium [3] (Table 1).

To meet the criteria of the more severe clinical TLS, one of the following clinical parameters must be present in addition: renal dysfunction, cardiac arrhythmia, seizures, or sudden death. There are 5 stages of severity [3] (Table 2).

What Are the Causes of TLS? Which Factors Play a Role?

In pathophysiological terms, tumor cell lysis generally occurs 12–72 h after initiating treatment with chemotherapeutic agents, antibody or immune therapies, targeted agents and glucocorticoids due to the rapid release of high amounts of intracellular components, which result in hyperkalemia, hyperphosphatemia, secondary hypocalcemia, hyperuricemia, and severe organ dysfunction [6]. Acute renal failure develops when the general compensation mechanisms for maintaining metabolic homeostasis fail. The acute renal failure is typically caused by obstructive urate nephropathy, triggered by uric acid precipitation in the tubular system [20].

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Table 3. Malignancies in which TLS prophylaxis is recommended due to the risk of TLS [2, 24, 25]

Low TLS risk	Intermediate TLS risk	High TLS risk
Most solid tumors [24, 25] • Non-small cell lung cancer • Breast cancer • Ovarian cancer • Vulvar cancer • Prostate cancer • Renal cell cancer • Hepatocellular cancer • Adenocarcinoma of the gastrointestinal tract • Malignancies • Rhabdomyosarcoma • Thymoma CLL and Lc <50 × 10^9/L treated with alkylating agents AML and Lc <25 × 10^9/L and LDH increase to <2× ULN MM CML Indolent NHL ALCL	Solid tumors with high tumor burden, advanced tumor stage, and high chemosensitivity • Small-cell lung cancer • Germ cell tumors • Neuroblastoma CLL treated with fludarabine, rituximab or lenalidomide or venetoclax and LN >5 cm or absolute lymphocyte count >25 × 10^9/L and/or Lc >50 × 10^9/L AML and Lc 25–100 × 10^9/L AML and Lc <25 × 10^9/L and LDH increase to >2× ULN T-cell leukemia/lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma, each with low tumor burden and elevated LDH and ALL and Lc <100 × 10^9/L and LDH increase to <2× ULN Burkitt's lymphoma and LDH increase to <2× ULN Lymphoblastic lymphoma stage I/II and LDH increase <2× ULN	Malignancies with intermediary risk and renal insufficiency Malignancy with intermediary risk and elevated serum parameters uric acid, potassium, and/or phosphate CLL treated with venetoclax and LN >10 cm or LN >5 cm absolute lymphocyte count >50 × 10^9/L and elevated uric acid AML and Lc 100 × 10^9/L T-cell leukemia/lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma with high tumor burden and LDH increase >2× ULN ALL and Lc >100 × 10^9/L and/or LDH increase >2× ULN Burkitt's lymphoma stage III/IV and/or LDH increase >2× ULN Burkitt leukemia Lymphoblastic lymphoma stage III/IV and/or LDH increase >2× ULN

CML, chronic myeloid leukemia; MM, multiple myeloma; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukemia; Lc, leukocytes; LN, lymph nodes; NHL, non-Hodgkin lymphoma.

How Can the Risk of TLS Be Detected?

In the development of TLS, a distinction is made between tumor-specific and tumor-independent risk factors [3, 4, 6, 20]. Tumor-associated factors generally include tumors with a high proliferation rate, a large tumor load, and pronounced chemosensitivity (pediatric tumors, germ cell tumors, small-cell lung cancer), which favor the development of TLS. In particular, these include acute lymphoblastic leukemia and aggressive non-Hodgkin's lymphoma, such as Burkitt's lymphoma [21] (Table 3).

Markers for large-scale cell death include tumor and lymph nodes in sizes exceeding 10 cm, leukocytosis (>500,000/μL), LDH increases to over twice the reference range, as well as organ and bone marrow infiltration at the time of diagnosis. There are also predisposing tumor-independent factors, such as advanced age, pre-existing renal dysfunction, oliguria, anuria, hyperuricemia, dehydration, deviations from normal urine pH value (low pH value: risk of urate nephropathy; high pH value: risk of calcium phosphate precipitation [22]), and concomitant administration of potentially nephrotoxic drugs [6]. The use of these criteria to identify at-risk patients is the first step for managing TLS. According to Cairo et al. [3], a distinction is made between low-risk, intermediate-risk, and high-risk groups. Preventive measures are guided by the identified risk as described below.

Which Prophylactic Measures Are Available?

If a patient is at increased risk of developing TLS, the first priority is to prevent the onset of TLS [2]. Basic measures for patient monitoring include daily logging of fluid intake and output, daily weight checks and close laboratory controls, specifically for uric acid, potassium, calcium, creatinine, phosphate, blood glucose, LDH and INR value. In addition, medication lists should be carefully reviewed and the administration of nephrotoxic substances should be avoided.

Regardless of the risk group, any therapeutic measures must be based on adequate intravenous patient hydration with a fluid supply of 2–4 L/day. The recommendations for selecting intravenous fluids vary [4]. Both sodium chloride and Ringer's lactate can be used. In patients with comorbidities, such as diabetes mellitus or heart failure, hydration should be monitored to avoid pulmonary edema.

The aim is to increase urinary excretion with a subsequent dilution effect of dissolved uric acid in the renal tubular system. Loop diuretics are used for forced diuresis, as they have a potent diuretic effect and flush out potassium. The target urine quantity is 80–100 mL per hour [6]. Hydration should be continued as long as signs of tumor cell death are evident [2, 9, 10, 22].

Which Therapeutic Measures Are Available for Treating Clinical TLS?

Hyperuricemia

Treatment with the urostatic drug allopurinol should be started 24–48 h before initiating chemotherapy. The recommended dose is 300–600 mg orally. Allopurinol intervenes in the DNA catabolism, where it competitively and reversibly inhibits the enzyme xanthine oxidase to prevent the degradation of hypoxanthine and xanthine nucleic acids. As a result, a smaller quantity of poorly soluble uric acid is formed and the water-soluble xanthine and hypoxanthine can be excreted through the kidneys. The dosage should be reduced in patients with kidney disease [23]. The advantages of this therapeutic measure are low cost and oral administration, while its disadvantage is a delayed onset of action by 24–72 h. As a result, allopurinol can only be used to a limited extent in the presence of high uric acid levels (≥476 μmol/L). The increased xanthine and hypoxanthine volumes also make it necessary to consider the risk of xanthine-induced renal failure as a differential diagnosis [4, 7, 23].

In contrast to allopurinol, rasburicase causes a rapid drop in uric acid without delay. The recombinant enzyme cleaves the uric acid into allantoin, a significantly more water-soluble nucleic acid. Further advantages of this drug include rapid onset and good tolerability [4, 6]. In both the study by Cortes et al. [26] and the meta-analysis by Lopez-Olivo et al. [27], rasburicase was found to be more effective for reducing uric acid levels. However, this had no effect on a better outcome in terms of clinically manifest TLS. The authorized dosage scheme is 0.15–0.20 mg/kg/day as a single intravenous infusion for 5–7 days. Some studies have shown that a weight-independent single dose of rasburicase had the same effect as extended therapy in most patients [28–30]. The use of rasburicase is contraindicated in the presence of known glucose-6 phosphate dehydrogenase deficiency since severe hemolytic anemia may develop as a consequence of hydrogen peroxide formation [6, 31].

Hyperkalemia

Hyperkalemia remains the most dangerous electrolyte abnormality in the context of TLS due to the risk of life-threatening cardiac arrhythmia [6]. Depending on the severity, a number of therapeutic measures are available [32]. An increase of serum potassium >7 mmol/L represents a medical emergency and requires immediate action. The intravenous administration of insulin and glucose or β-2 mimetics cause an intracellular potassium shift, while calcium gluconate leads to the additional stabilization of cardiac membranes. However, this frequently only achieves a temporary effect, and renal replacement therapy is needed.

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Hyperphosphatemia/Hypocalcemia

Any existing hyperphosphatemia should be corrected. It is best to treat moderate hyperphosphatemia with a low-phosphate diet and phosphate binders [32]. Since electrolyte imbalances can be difficult to manage with drug therapy in spite of all measures, renal replacement therapy should therefore be prescribed in the majority of cases [6, 22, 33].

Hyperphosphatemia causes secondary hypocalcemia, which reinforces cardiac arrhythmia tendencies and can also cause tetany, muscle cramps, and seizures. Due to the risk of calcium phosphate deposits, it is best not to treat asymptomatic hypocalcemia, while manifest hypocalcemia should be treated with the lowest possible calcium gluconate dose until the symptoms abate [6, 22].

Indication of Renal Replacement Therapy

In spite of the best prevention and therapy, some patients develop serum electrolyte imbalances that cannot be treated conservatively as well as acute renal failure. Dialysis is indicated in these cases [6]. The chances of full renal function recovery are good, provided the renal replacement therapy is initiated early and leads to an adequate reduction of uric acid and phosphate levels.

Absolute dialysis indications are severe oliguria or anuria, therapy-resistant hyperkalemia and hyperphosphatemia, and symptomatic hyperphosphatemia-induced hypocalcemia [7, 22, 34].

Conclusion

Spontaneous TLS is a rare hemato-oncological emergency situation. Patients with elevated tumor-associated and individual risk should be identified as such and must be closely monitored for clinical and laboratory parameters [14]. This allows for the early initiation of preventive measures and can have a positive influence on the clinical course. Manifest TLS, on the other hand, generally requires intensive therapy.

Statement of Ethics

For this paper, the authors did not conduct any studies in humans or animals. The ethical guidelines for the studies listed apply to the respective studies. The patient has given his informed consent to the publication of the present case report including the publication of images.

Conflict of Interest Statement

The authors state that there is no conflict of interest.

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Author Contributions

The corresponding author wrote the entire article, researched the literature, evaluated this literature in the discussion, and wrote the tables. The co-author has read the article and provided suggestions for correction. No other persons were involved.

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