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A case of spontaneous tumor lysis syndrome in extensive-stage small-cell lung cancer: A rare oncologic emergency

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Abstract:

Tumor lysis syndrome (TLS) is an oncologic emergency. It generally occurs after chemotherapy but sometimes develops spontaneously in hematologic malignancy, such as leukemia. TLS is a rare phenomenon in patients with solid tumors, particularly when it develops spontaneously. Here, we present a case of spontaneous TLS (STLS) in a patient with small-cell lung cancer (SCLC). We report a case of STLS in a 59-year-old male patient who presented with dyspnea and oliguria. Clinicians should suspect TLS in patients with malignancy, who demonstrate the classic electrolyte abnormalities of TLS even if not receiving treatment such as chemotherapy or radiotherapy.

Keywords:

Acute renal failure, emergency treatment, hyperuricemia, small-cell lung carcinoma, tumor lysis syndrome

Introduction

Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency. It is characterized by metabolic and electrolyte abnormalities, such as hyperphosphatemia, hyperkalemia, hyperuricemia, and hypocalcemia, secondary to the release of intracellular ions and nucleic acid metabolites into the bloodstream. This situation can lead to acute renal failure, cardiac dysrhythmia, seizures, and death.^[1] TLS usually occurs in hematologic malignancies with a high proliferative rate after the initiation of treatment. The incidence of TLS in hematological malignancies is reported as 4%–42%. However, it is much less frequent with solid tumors.^[2] Spontaneous TLS (STLS) has

been defined in hematologic malignancies, especially Burkitt's lymphoma and acute lymphoblastic leukemia.^[3] The incidence of STLS in solid tumors is not known, but it is thought to be very rare.^[4] To our knowledge, only eight cases of STLS in small-cell lung carcinoma (SCLC) have been published in the medical literature. Herein, we report a patient diagnosed with extensive-stage SCLC who developed STLS, and we review the literature of the eight previously reported cases.

Case Report

A 59-year-old male patient who had chronic obstructive pulmonary disease presented to the emergency department with generalized fatigue, dyspnea, and oliguria. His vital signs were unstable, with a blood pressure of 70/40 mmHg, pulse rate of 122 bpm, a temperature of 36.4°C, and peripheral

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oxygen saturation of 88% (on room air). His physical examination revealed decreased breath sounds in the lower right lung fields, pretibial edema (++), and hepatomegaly. His laboratory results were as follows: serum potassium 6.0 mEq/dL, phosphorus 5.2 mg/dL, alanine aminotransferase 672 U/L, alkaline phosphatase 489 U/L, total bilirubin 1.6 mg/dL, direct bilirubin 0.87 mg/dL, lactate dehydrogenase (LDH) 2954 U/L, creatinine (Cr) 2.15 mg/dL (baseline Cr 0.9 mg/dL), uric acid 20.32 mg/dL, serum calcium level 10.2 mg/dL, albumin 3.0 g/dL, and C-reactive protein 115 mg/L. Chest radiography showed wide and irregular round opacity in the lower right zone. We discovered from the history of the patient taken from family members that the pulmonary medicine department suspected and examined the patient for cancer at the outpatient clinic. The official radiology reports of the thoracoabdominal computed tomography scan performed a week ago revealed an 11 cm × 9 cm × 8 cm solid mass neighboring to heart with surrounding atelectasis, mediastinal lymphadenopathies, and multiple liver metastases [Figure 1]. We also learned that a biopsy was conducted on the mass with bronchoscopy 3 days ago.

We admitted the patient to the intensive care unit with the diagnosis of TLS. We initiated intravenous (IV) fluid hydration 200 ml/h, antipotassium treatment (insulin infusion and potassium binders), and allopurinol according to the TLS treatment guidelines. Blood and urine cultures were drawn, and meropenem 2 g/day was initiated since septic shock could not be ruled out. We were unable to start rasburicase since it was not available in our country. Serial laboratory examinations showed increases in the levels of Cr, potassium, and phosphorus [Table 1]. We consulted with the nephrology department, and hemodialysis was initiated. Official pathology reports confirmed the working diagnosis of SCLS. Unfortunately, we lost our patient on the 3rd day in the intensive care unit.

We obtained written informed consent of the patient's family for the publication of his case and any accompanying images.

Discussion

TLS is an oncological emergency that develops after the initiation of treatment in hematological malignancies (Burkitt's lymphoma and acute lymphoblastic leukemia) and rarely reported in solid tumors. It is commonly seen in patients with highly chemosensitive tumors or in patients with a massive tumor burden.^[5] TLS develops as a result of the release of intracellular contents into the blood due to the massive destruction of tumor cells, causing severe metabolic abnormalities such as hyperkalemia,

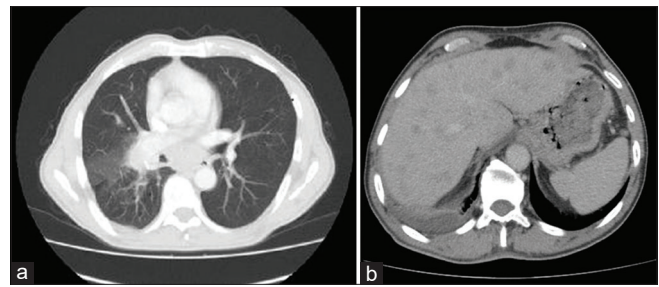


Figure 1: Computed tomographic scan of thoracoabdominal showing (a) the mass in the lung and (b) multiple metastatic nodules in the liver

Table 1: Laboratory examination results of the patient on days 1-3

Parameters (N)	Day 1	Day 2	Day 3
Urea (mg/dL) (17-43)	215	202	241
Creatinine (mg/dL) (0.8-1.4)	2.15	2.02	2.19
Uric acid (mg/dL) (3.5-7.2)	20.3	19.2	17.6
Potassium (mmol/L) (3.5-5.1)	6.9	6.8	7.1
Phosphorus (mg/dL) (2.5-4.5)	5.2	6.2	7.2
Calcium (mg/dL) (8.6-10.8)	10.2	9.8	9.6
ALT (U/L) (0-50)	672	824	986
LDH (U/L) (0-248)	2954	3277	5450
Total bilirubin (mg/dL) (0-1.22)	1.26	1.5	1.63
C-reactive protein (mg/L) (0-5)	111	115	139
Venous blood pH (7.3-7.45)	7.21	7.23	6.82
Sodium bicarbonate (mEq/L) (22-26)	14.7	15.4	4.9
Lactic acid (mmol/L) (0.5-2.2)	7.3	7.2	9.1

N=Normal range, ALT=Alanine aminotransferase, LDH=Lactate dehydrogenase

hyperphosphatemia, hyperuricemia, and hypocalcemia. These metabolic disorders can cause clinical toxic effects, including acute kidney injury, seizures, cardiac arrhythmias, or even death. We classify TLS as laboratory and clinical TLS by Cairo and Bishop's Classification System. Laboratory TLS necessitates the presence of at least two of the following metabolic abnormalities 3 days before or up to 7 days after the initiation of the therapy (potassium ≥ 6 mmol/L or 25% increase from baseline; phosphorus ≥ 4.6 mg/dL or 25% increase from baseline; calcium ≤ 7.0 mg/dL or 25% decrease from baseline; uric acid ≥ 8.0 mg/dL or 25% increase from baseline). Clinical TLS is described as increased serum Cr, cardiac arrhythmia, seizure, or death associated with laboratory TLS.^[1]

TLS that develops before the initiation of any treatment is defined as STLS and is more commonly associated with hematologic malignancies, similar to TLS.^[3] It is very rare in solid tumors, and only a few cases were reported in the literature in patients with germ cell tumors, squamous cell lung cancer, gastric cancer, and metastatic melanoma.^[6,7] We were able to locate only eight cases of STLS in SCLS, in our literature search. Jallad *et al.* reported the first STLS patient, a 75-year-old patient with metastatic SCLS. All eight published patients of STLS in SCLC are summarized in Table 2.^[8-14]

Table 2: Cases of spontaneous tumor lysis syndrome in small cell lung cancer

Authors (published year)	Patient	Tumor burden	Treatment	Outcomes
Jallad <i>et al.</i> (2011) ^[8]	75-year-old female	Liver metastasis	None	Exitus
Padhi and Singh (2012) ^[9]	73-year-old female	Liver metastasis	Hydration	Exitus
Weerasinghe <i>et al.</i> (2015) ^[10]	65-year-old male	Bone metastasis Liver metastasis Multiple lymphadenopathies	Hydration Rasburicase Allopurinol Chemotherapy	Survival
Martínez <i>et al.</i> (2016) ^[11]	64-year-old male 60-year-old male	Liver metastasis	Hydration Rasburicase	Exitus
Kanchustambham <i>et al.</i> (2017) ^[12]	53-year-old male	Lymphadenopathy	Hydration Rasburicase Chemoradiotherapy	Survival
Dean <i>et al.</i> (2018) ^[13]	76-year-old female	Liver metastasis	Hydration Rasburicase	Exitus
Dhakal <i>et al.</i> (2018) ^[14]	70-year-old-male	Liver metastasis	Hydration Rasburicase Allopurinol Hemodialysis	Exitus
Our case	59-year-old male	Liver metastasis	Hydration Allopurinol Hemodialysis	Exitus

Seven of those patients had multiple liver metastases. The median age was 67 years (range: 53–73), and the median LDH was 1196 U/L (range: 399–3350) on presentation. All patients were lost during the disease period, except for two. We do not know the specific risk factors of STLS and the patients who should receive prophylactic measures since the etiopathogenesis of STLS in solid tumors is still unclear. Necrosis of the bulky tumor masses due to insufficient blood flow may trigger the pathogenic cascade of STLS. Further, the activation of inflammation as a result of necrosis could initiate a systemic inflammatory response and contribute to the occurrence of STLS.^[4,5] However, based on the current case reports in the literature, multiple liver metastases, advanced age, or elevated LDH levels may be considered as risk factors for the development of STLS in patients with SCLC.

Hydration is the cornerstone approach of preventing TLS and is advised before treatment in all patients who had high risk for TLS. Current guideline recommends that adults who had the risk for TLS receive 2–3 L/m² IV fluid/day. On the other hand, the use of sodium bicarbonate for urinary alkalinization is controversial yet suggested in patients with metabolic acidosis. Hypouricemic agents (allopurinol and rasburicase, a recombinant urate oxidase inhibitor) can be used according to the risk profile of the patients. The patient who developed TLS spontaneously or during treatment should be treated with intensive supportive care. Cardiac and urinary monitorization and measurement of electrolytes, Cr, and uric acid every

4–6 h should be performed. As hyperkalemia may cause sudden death due to cardiac dysrhythmias, it is the electrolyte abnormality that needs to be treated as quickly as possible in TLS. Glucose with insulin infusion, beta-agonist inhalation, and oral potassium-binding agents may be used to lower the potassium level. Further, calcium gluconate can be utilized to reduce the risk of cardiac dysrhythmia. Treatment of hyperphosphatemia is limited to the restriction of phosphorus intake and the use of phosphate-binding agents. Calcium replacement should be avoided in patients with asymptomatic hypocalcemia because it may cause calcium phosphate precipitation within kidneys. However, calcium replacement should be performed in patients with severe symptoms of hypocalcemia regardless of the phosphate level. Allopurinol is a xanthine oxidase inhibitor that effects by preventing the formed of uric acid crystals in the renal tubules. Nevertheless, it cannot break already deposited uric acid crystals down. Therefore, while allopurinol is useful in the prophylactic setting, its efficacy in the treatment of TLS is limited. Rasburicase, which is a recombinant urate oxidase, metabolizes urate directly to the more water-soluble compound allantoin. It can break down crystals of uric acid and reduce its levels significantly more quickly than allopurinol. The standard recommended dose of rasburicase is 0.2 mg/kg/day (30-min IV infusion). Current guidelines recommend that it can be performed for 3–7 days with close monitoring. Despite optimal intensive treatment, hemodialysis may be required in some patients who had severe acute

kidney injury (severe oliguria or anuria, persistent hyperkalemia, hyperphosphatemia-induced symptomatic hypocalcemia, and a calcium phosphate product ≥ 70 mg/dL).^[4,5,15]

Our patient had elevated uric acid (20 mg/dL), phosphorus (5.2 mg/dL), potassium (6.9 mmol/L), and Cr (2.15 mg/dL). As he had three of the metabolic abnormalities and acute kidney injury, he had diagnosed clinical and laboratory TLS. Although we performed aggressive treatment and subsequent hemodialysis, the patient died due to STLS. Our patient had liver metastasis and elevated LDH, as seen in the other seven patients with STLS. In contrast to the other eight case reports, in our case, STLS occurred 3 days after a biopsy was conducted with bronchoscopy. We think that the bronchoscopy procedure may have triggered the development of TLS. However, to the best of our knowledge, there are no such cases reported in the literature.

Conclusion

TLS is an oncologic emergency that can arise as a result of treatment, or rarely spontaneously. We present a case of STLS in SCLC that is also quite rare. TLS in solid tumors has a high mortality. Recognition of patients and early initiation of aggressive treatment is crucial and can prevent significant morbidity and mortality. Therefore, clinicians should be aware of this rare phenomenon.

Consent to participate

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Author contribution statement

AMA contributed to clinical management of the case, manuscript editing, final approval, and corresponding author. OA contributed to the evaluation of patients' follow-up, design of the writing, and support of the literature.

Conflicts of interest

None declared.

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