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Tumor Lysis Syndrome in Chronic Lymphocytic Leukemia: A Rare Case Report from Nephrology

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 **Zaher Armaly**
ACDE 2 **Mazen Elias**
B 3 **Rabah Yasin**
BC 1 **Munir Hamzeh**
BC 4 **Adel R. Jabbour**
BCE 5 **Suheil Artoul**
BC 3 **Amer Saffouri**

1 Department of Nephrology, EMMS Hospital, Affiliated to The Azrieli Faculty of Medicine in Galilee, Bar-Ilan University, Nazareth, Israel
2 Department of Internal Medicine B, HaEmeq Hospital Affiliated to The Faculty of Medicine, Technion, Afula, Israel
3 Department of Internal Medicine, EMMS Hospital, Affiliated to The Azrieli Faculty of Medicine in Galilee, Bar-Ilan University, Nazareth, Israel
4 Department of Laboratory Medicine, EMMS Hospital, Affiliated to The Azrieli Faculty of Medicine in Galilee, Bar-Ilan University, Nazareth, Israel
5 Department of Radiology, EMMS Hospital, Affiliated to The Azrieli Faculty of Medicine in Galilee, Bar-Ilan University, Nazareth, Israel

Corresponding Author: Zaher Armaly, e-mail: zaherarmaly@nazhosp.com
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Patient: Female, 89
Final Diagnosis: Tumor lysis syndrome (TLS)
Symptoms: Dyspnea
Medication: Steroids
Clinical Procedure: HD
Specialty: Nephrology

Objective: Unusual clinical course



Background: Tumor lysis syndrome is common in hematological malignancy, but less frequent in chronic and solid tumors. Almost always it is observed after chemotherapy or radiotherapy initiation, but rarely occurs spontaneously.

Case Report: A 89-year-old female with stable chronic lymphocytic leukemia was admitted to the hospital because of worsening dyspnea and dry cough. Her vital signs were normal, except for sinus tachycardia. On physical examination, she appeared distressed, dyspneic, sweaty but afebrile, anxious, but alert and well oriented. Lung examination revealed reduced air entry with bibasilar crackles. No peripheral edema was seen, pulses were normal, and no signs of deep vein thrombosis were observed. Laboratory analysis revealed leukocytosis; but normal hematological and biochemical parameters. Intravenous (IV) furosemide and antibiotics (IV ceftriaxone and orally azithromycin) were started along with steroid therapy (methylprednisolone 62.5 mg, IV). The treatment with steroids lasted for 1 day only, and in the following day, the patient was switched to prednisone (20 mg/day orally) for only 1 additional day. White blood cell count increased on day 1, 2 and 3 after admission, along development of hyperuricemia, hyperphosphatemia, hyperkalemia, acute renal failure and elevated troponin levels. Hemodiafiltration/hemodialysis was initiated, and the patient was discharged after serum concentrations of these electrolytes and kidney function were restored. One month after discharge, the patient denied any malaise and was at stable condition.

Conclusions: Herein, we present a case of a patient with stable chronic lymphocytic leukemia, who developed spontaneous tumor lysis syndrome after short low dose of steroid therapy. This case highlights the importance of including spontaneous tumor lysis syndrome in the differential diagnosis of any acute renal failure in the constellation of any malignancy.

MeSH Keywords: Acute Kidney Injury • Hemodialysis Units, Hospital • Leukemia, Lymphocytic, Chronic, B-Cell • Tumor Lysis Syndrome

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Background

Tumor lysis syndrome (TLS) is a life threatening oncologic and nephrologic complication of acute hematological malignancy [1–5], but less frequent in chronic and solid tumors [6–9]. Usually it is observed after chemotherapy or radiotherapy initiation, but rarely occurs spontaneously (STLS) [10–16]. TLS is characterized by the release into the systemic circulation of several intracellular components following lysis of tumor cells, with consequent hyperkalemia, hyperphosphatemia, hyperuricemia, hypermagnesemia and hypocalcemia [3,17,18]. If left untreated these aberrancies in electrolyte balance may lead to death from fatal arrhythmias, seizures and severe acute renal failure [1,2,4,5,19].

Case Report

We report a case of an 89-year-old female known to suffer from stable chronic lymphocytic leukemia (CLL) for more than 40 years, without any related treatment for the last 15 years. She was otherwise in relatively good health with no history of hypertension, coronary disease, recurrent infections or hospitalization.

Her usual white blood cell (WBC) counts were approximately $12\text{--}15 \times 10^3/\mu\text{L}$ and her hemoglobin levels were 12 g%. Kidney function was normal as was evident by serum creatinine (Scr) of 0.76 mg/dL (eGFR=66.4 mL/min, according to CKD-EPI) (Table 1). Her body mass index (BMI) was 18 kg/m².

She was admitted to the hospital because of worsening dyspnea and dry cough. Prior to her admission, she was treated with antibiotic (azithromycin 250 mg twice daily) for 1 week due to upper respiratory tract infection (URTI).

She denied fever, chest pain, gastrointestinal or urinary symptoms. Her vital signs were normal, except for sinus tachycardia 112 beats/min.

On physical examination, she appeared distressed, anxious, but alert and well oriented. She was dyspneic (RR 36 breaths/min), sweaty but afebrile. There was no rash, pharyngitis, or signs of sinusitis.

Heart sounds were normal. Lung examination revealed reduced air entry with bibasilar crackles. Palpable axillary lymphadenopathies were found. Abdomen was soft without organomegaly. No peripheral edema was seen, pulses were normal, and no signs of deep vein thrombosis were observed.

Laboratory tests on admission

WBC $67 \times 10^3/\mu\text{L}$, neutrophils 5%, lymphocytes 78%, hemoglobin (Hb) 11.2 g%, hematocrit (Hct) 33, platelets $72 \times 10^3/\mu\text{L}$, serum creatinine 0.76 mg/dL, potassium 4.9 mEq/L, blood sugar 122 mg/dL, blood urea nitrogen (BUN) 24 mg/dL, calcium 8.9 mg/dL, phosphorus 4 mg/dL, albumin 4.6 g/dL (normal range 3.5–5.2), total protein 6.5 g/dL (normal range, 6.6–8.3), C-reactive protein (CRP) 0.9 mg/L (normal range 0–0.5), and liver enzymes and lipid profile were normal (Table 1). Uric acid and lactate dehydrogenase (LDH) were not available.

Venous blood gases: pH 7.32, partial pressure of carbon dioxide (pCO₂) 51 mmHg, bicarbonate (HCO₃) 26 mmol/L.

Chest x-ray (CXR) revealed enlarged cardiac silhouette, pulmonary congestion, and an infiltration in the left lower lobe, which consisted with pneumonia or as part of the congestion (Figure 1).

Intravenous (IV) furosemide and antibiotics (IV ceftriaxone and oral azithromycin) were started along with IV steroids therapy (methylprednisolone 62.5 mg) for upper respiratory infection (URI). The treatment with antibiotics lasted for 1 week and steroids lasted for 1 day only, and in the following day, the patient was switched to prednisone (20 mg/day orally) for only 1 additional day.

On day 1 of her admission, CXR was improved and no more lung infiltration was seen. *Staphylococcus Epidermidis* was

Table 1. Progression of the patient's electrolyte derangements.

| Lab Variable | On admission | Day 1 | Day 2 | Day 3 | At Discharge | After 30 days | Reference range |
|-----------------------------------|--------------|-------|-------|-------|--------------|---------------|-----------------|
| WBC ($\times 10^3/\mu\text{L}$) | 67 | 157 | 135 | 190 | 94 | 12 | 4.5–11.5 |
| Uric acid (mg/dL) | – | – | 20.4 | 42.5 | 9.7 | 5.6 | 2.6–6.0 |
| Potassium (mg/dL) | 4.9 | 5.1 | 4.6 | 6.94 | 3.8 | 4.6 | 3.5–5.1 |
| Phosphorus (mg/dL) | 4.9 | – | 7.8 | 26.3 | 2.6 | 3.8 | 2.5–5.0 |
| Creatinine (mg/dL) | 0.76 | 0.69 | 1.63 | 2.2 | 0.78 | 0.44 | 0.51–0.95 |
| BUN (mg/dL) | 24 | 27 | 55 | 107 | 39 | 21 | 8.5–21.5 |
| LDH (U/L) | – | – | 966 | 1135 | 694 | 645 | 230–480 |

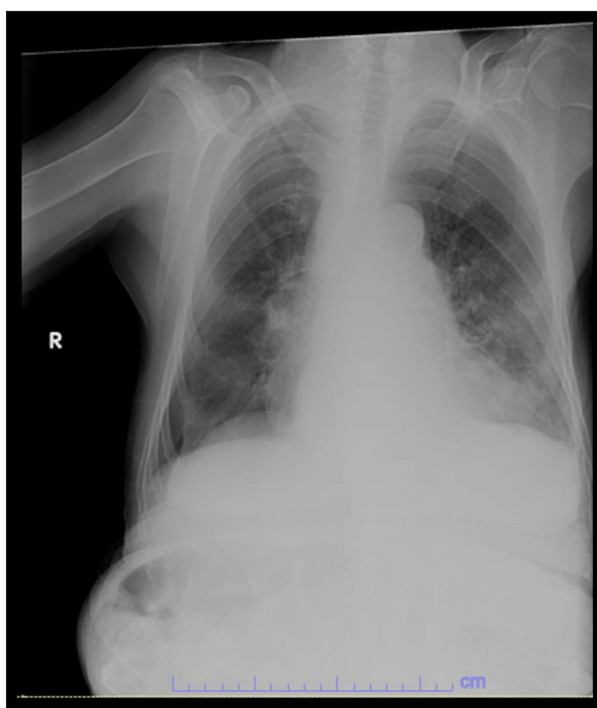


Figure 1. Anterior chest x-ray demonstrating enlarged cardiac silhouette, pulmonary congestion and an infiltration in the left lower lobe.

grown in the first blood culture, but no further growth was seen in the following blood cultures, and so the first culture was considered to be a contamination. Urine antigen (Ag) for Legionella and *Streptococcus Pneumoniae* were also negative.

WBC $157 \times 10^3/\mu\text{L}$, lymphocytes 69%, neutrophils 4%, Hb 12.1 g%, Hct 36, platelets $129 \times 10^3/\mu\text{L}$, serum creatinine 0.69 mg/dL, potassium 5.1 mEq/L, blood sugar 146 mg/dL, and BUN 27 mg/dL. The IgG level was slightly low 640 (normal range 650–1500) (Table 1), so IV immunoglobulin (IVIg) was postponed in the absence of pneumonia. She also developed silent non-ST elevation myocardial infarction (NSTEMI) with troponin elevation from 60 (on admission) to 2600 ng/L. There were no ischemic changes in the electrocardiogram, and conservative treatment was advised by the cardiologic consult by adding aspirin and clopidogrel.

On day 2, the patient developed oliguric acute renal failure (100 mL/24 hours), with serum creatinine 1.63 mg/dL, BUN 55 mg/dL, perfusion index (Pi) 7.8 mg/dL, magnesium (Mg) 2.9 mg/dL, uric acid 20.4 mg/dL, calcium 8.3 mg/dL, WBC $135 \times 10^3/\mu\text{L}$, platelets $129 \times 10^3/\mu\text{L}$, Hb 12.1 g/dL, LDH 966 U/L, pH 7.30, and HCO_3^- 17 mEq/L (Table 1). A diagnosis of tumor lysis syndrome (TLS) was raised as a differential diagnosis, despite not having any prior knowledge whether CLL can be complicated by TLS without any chemotherapy, radiotherapy, high dose steroids therapy or evolution to Richter's syndrome.

The latter is a clinical condition in which CLL changes into a fast-growing type of lymphoma. Conservative treatment as a first step therapy was instituted by giving intravenous fluids along with bicarbonate in the presence of metabolic acidosis. In addition, febuxostat (80 mg/day) as well as sevelamer (2.4 g/day) were initiated.

On day 3, the patient became anuric with further deterioration of blood tests: Pi 26 mg/d, uric acid 42 mg/dL, calcium 7.2 mg/dL, magnesium 3.55 mg/dL, LDH 966 u/L, BUN 107 mg/dL, serum creatinine 2.2 mg/dL, sodium 133 meq/L, potassium 6.94 mmol/L, LDH 1135 U/L, pH 7.30, HCO_3^- 16 mmol/L, pCO_2 45 mmHg, AG 21, WBC $190 \times 10^3/\mu\text{L}$, lymphocytes 64%, neutrophils 5%, Hb 9.6 g/dL, and platelets $166 \times 10^3/\mu\text{L}$ (Table 1).

A diagnosis of TLS was confirmed, and urgent long hemodialysis was initiated. A total of only 3 consecutive sessions of initially hemodialysis followed by hemodiafiltration were sufficient to achieve a full recovery of kidney functions and electrolytes balance. Her serum creatinine was 0.78 mg/dL, BUN 39 mg/dL, calcium 7.5 mg/dL, Pi 2.6, LDH 694 U/L, uric acid 9.7 pH 7.43, HCO_3^- 25.5, and pCO_2 39 (Table 1).

The patient was discharged home with a hemodynamically stable condition.

1 month later, her WBC was $12 \times 10^3/\mu\text{L}$, lymph 69%, platelets $103 \times 10^3/\mu\text{L}$, serum creatinine 0.44 mg/dL, BUN 21 mg/dL, potassium 4.6 mEq/L, Pi 3.8 mg/dL, calcium 8.2 mg/dL, uric acid 5.6 mg/dL, and LDH 645 U/L (Table 1).

Discussion

TLS is a well-recognized both nephrologic and oncologic emergency and an urgent treatment is needed accordingly. If an immediate treatment is not instituted this complication can end with death [2,15,20].

TLS is usually seen in highly proliferative malignant lymphomas, leukemia (such as Burkitt's lymphoma and acute lymphoid leukemia) [1,2] after cytotoxic chemotherapy and radiotherapy initiation [3]. Less frequently, TLS is seen after high dose steroid therapy [4,16], or even before initiation appropriate therapy [19].

In chronic hematologic malignancies, TLS is rarely observed [5,6,10] as well as in solid malignancies [7,8]. This is due to both slow rate of proliferation and response to chemotherapy. However, in highly proliferative and bulky chemosensitive tumors, spontaneous TLS (STLS) can be seen [11–14,17,18,21,22].

Nowadays, even these chronic malignancies showed an increased frequency of TLS owing to new target therapies [15,20].

TLS is characterized by the release into the systemic circulation of several intracellular components such as potassium, phosphorous, nucleic acids, and magnesium from lysis of tumor cells, with consequent hyperkalemia, hyperphosphatemia, hyperuricemia, hypermagnesemia and hypocalcemia, as in our case [2,23]. If left untreated, these aberrancies in electrolyte balance may lead to death due to fatal arrhythmias, neurologic complications (seizures) and chronic dialysis due to end stage renal disease (ESRD) [3,15,20,23].

Our patient meets both the Cairo-Bishop criteria [11] as well as the Howard criteria [2] for TLS. The Cairo-Bishop criteria requires 2 or more defined laboratory abnormalities with a 25% change from baseline occurring at any time within 3 days prior or 7 days after chemotherapy [20], and the Howard criteria which is a modification of the Cairo-Bishop criteria, omits the need for a 25% change in laboratory values and instead adds that the 2 or more defined laboratory abnormalities (based on absolute values) must present within a 24-hour period to meet the definition of laboratory TLS [2].

Herein we present a rare case in the literature that describes a STLS in a stable CLL patient, which later quickly resolved after only 3 sessions of hemodialysis without any sequelae. Similar findings were reported by Tufan et al. [19], who described spontaneous TLS in a patient with diffuse large B cell lymphoma and Richter syndrome (RS). The latter is a clinical condition in which CLL changes into a fast-growing type of lymphoma that could be the same process described in the present case. Specifically, diffuse large B cell lymphoma may develop into RS following CLL. Development of RS was reported in about 2.2% to 8% of cases during the clinical course of CLL [24].

However, we could not exclude that the administration of steroids even in very small dose for 2 days triggered TLS in our patient. In this context, Coutinho et al. [16] reported TLS in a case of CLL 48 hours following treatment with high-dose corticosteroids (2 doses of 2 gr methylprednisolone). Likewise, Vaisban et al. [4] reported a case of TLS in patient with CLL that

was treated by high dose corticosteroids. Although TLS was described in high-grade lymphoproliferative disorders after the use of corticosteroids, our case along those of Coutinho [16] and Vaisban [4] are the only reports in the literature of TLS induced by corticosteroids used as a single agent in CLL. However, the present case is the first one to show that administration of even low steroid doses for short period to CLL patients may cause TLS. Unfortunately, the mechanisms underlying steroids induced LTS in CLL is unknown, and additional studies in this regard are needed. However, the cytotoxic action of the glucocorticoids is thought to be mediated by specific cytoplasmic receptors, via which the steroids form a complex [25]. Glucocorticoids have been shown to damage lymphoid cells by a number of pathways: including inhibition of DNA synthesis changing the membrane structure and cytolysis [25].

The rarity of this complication should prompt us to consider it in future cases of CLL. Furthermore, this case emphasizes the importance of continued awareness and prompt treatment.

Conclusions

Herein, we present a rare case of a patient with stable CLL, who developed either STLS or steroid-induced TLS. As STLS has never been reported in a patient with CLL, we could not exclude that this phenomenon developed due to steroid administration even at low doses. This case highlights the importance of including STLS/SLT in the differential diagnosis of any acute renal injury in the constellation of any malignancy.

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Conflicts of interest

None.

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