A rare case of spontaneous tumor lysis syndrome in multiple myeloma

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ABSTRACT
Spontaneous tumor lysis syndrome is an uncommon oncologic emergency. It occurs when a massive number of malignant cells release their contents to the blood stream without previous cancer treatment. TLS carries a mortality rate exceeding 15%. Because of the high mortality rate, the key to the management of TLS continues to be early recognition of high-risk patients and using prophylactic measures to prevent its occurrence. However, it remains difficult to completely eradicate TLS, as a small proportion of patients with aggressive tumors develop spontaneous TLS prior to receiving any therapy. We present a case of 58-year-old male with recently diagnosed multiple myeloma. He was found to have hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, elevated LDH levels, and acute renal failure, fulfilling the criteria of clinical TLS. He was treated with rasburicase, continuous renal replacement therapy, and dexamethasone.

1. Introduction
Tumor lysis syndrome (TLS) is characterized by a constellation of clinical and metabolic disturbances occurring as a result of rapid cellular death and release of intracellular contents. TLS occurs in 5%-20% of malignancies, typically occurring 48-72 hours after patients with high-grade rapidly proliferating hematologic malignancies initiate chemotherapy or targeted therapy [1]. Much less frequently, patients may have spontaneous TLS with a similar constellation of disturbances, which has been observed in aggressive lymphomas such as Burkitt’s lymphoma and with acute leukemias with markedly elevated cell counts [2]. Here we describe a case of spontaneous TLS from multiple myeloma, which is unusual in that it is considered an indolent hematologic malignancy.

2. Case presentation
A 58-year-old male presented with worsening lethargy, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea of 1-week duration and decreased urine output for the last 2-3 days prior to his presentation. His past medical history was significant for morbid obesity, gout, sarcoidosis, chronic right-sided heart failure, COPD on 3 L home oxygen, atrial fibrillation, chronic kidney disease, pulmonary hypertension, and obstructive sleep apnea. The patient presented to another hospital with acute or chronic hypoxic respiratory failure, acute renal failure, and hyperkalemia and was discharged 8 days prior to presentation at our hospital. Initial workup revealed Bence-Jones proteinuria lambda U at 7500 mg/dL, and a bone survey revealed a skull lesion. Bone marrow biopsy demonstrated diffuse marrow replacement by plasma cells accounting for nearly 85% of nucleated cells, consistent with multiple myeloma (Figures 1–4). Chromosomal analysis was normal. The patient was discharged with a plan to initiate treatment for multiple myeloma after discharge.

On presentation to our hospital, the patient’s temperature was 35.9 degrees Celsius, heart rate was 78 bpm, respiratory rate was 35 breaths per minute, blood pressure was 88/42 mmHg, and O₂ saturation on 6 L nasal cannula was 92%. The patient was lethargic and tachypneic using accessory muscles. He had evidence of congestive heart failure with cool and mottled extremities with reduced pulses. His labs demonstrated severe anemia with hemoglobin 7.4 mg/dL and platelets 102 k/uL, potassium 8.5 mEq/L, bicarbonate 17 mEq/L, calcium 6.4 mg/dL, phosphorus 13.2 mg/dL, BUN 152 mg/dL, creatinine 11.6 mg/dL, uric acid 19.4 mg/dL, and lactic acid 36.94 mg/dL. Transthoracic echocardiogram showed normal left ventricular size with estimated ejection fraction of 50%-55%. The right ventricle was severely enlarged and hypokinetic with flattening of the
intraventricular septum consistent with right ventricular failure and volume overload and moderately elevated pulmonary artery systolic pressure.

The patient was treated for shock and volume overload and started on continuous renal replacement therapy (CRRT), rasburicase, and dexamethasone. In less than 72 hours, the patient was extubated and transitioned to high-flow nasal canula. He was started on induction chemotherapy with bortezomib, cyclophosphamide, and dexamethasone. After initial treatment, the patient became markedly pancytopenic, hypotensive, and had worsening dyspnea. Due to the overall poor prognosis, the patient and his family decided to pursue comfort measures.

3. Discussion

TLS is considered a medical emergency, with hospital and 6-month mortality rates reaching 66% if it presents with acute renal injury [3]. The incidence of TLS in multiple myeloma is extremely low. It occurs

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Figure 1. Giemsa stained slide, 400X. Bone marrow aspirate smear with plasma cells. The characteristic morphology of the plasma cells is best seen on this preparation (eccentric nucleus, 'clockface' clumped chromatin, perinuclear 'hof' (area of clearing representing the location of the Golgi apparatus).

Figure 2. H&E stained slide, 100X. Bone marrow clot section with a fragment of crushed cellular marrow composed predominantly of plasma cells.
in approximately 1% of multiple myeloma patients receiving high-dose chemotherapy for stem cell transplantation [4]. There are only a few reported cases of TLS occurring spontaneously in multiple myeloma [5–8].

Some risk factors for developing TLS in multiple myeloma patients have been identified, such as hyperproliferative disease (as measured by plasmacyte labeling index), immature plasma cell morphology, circulating plasmablasts, unfavorable cytogenetics, and increased lactate dehydrogenase (LDH) [6]. LDH level has been found to correlate with multiple myeloma aggressiveness [9] and with the presence of occult extraosseous disease and high tumor mass [10]. Tumor burden, tumor size, and extensive bone marrow involvement are have been identified previously as predictors for development of TLS [11]. In a case series of 7 patients with TLS in MM, several abnormal karyotypes were found, with del 9p13, del 17, and monosomy 13f being the most frequent. However, no uniform abnormal karyotypes have been identified as risk factors for developing TLS [5]. Despite a normal chromosome analysis, we identified the presence of chronic kidney disease, the use of steroids, gout, and high tumor burden as potential risk factors for TLS in this case.

**Figure 3.** H&E stained slide, 400X. Bone marrow clot section with a higher power shot of the marrow fragment in Figure 2, showing a predominant component of plasma cells.

**Figure 4.** CD138 immunohistochemical stain, 100X. Bone marrow clot section of cellular marrow focus in Figure 3 with CD138 stain highlighting the abundant plasma cells.
Based on the report of an international TLS expert consensus panel in 2008, multiple myeloma is considered a low-risk tumor for developing TLS. Typically, normal hydration and no prophylaxis is needed for multiple myeloma patients unless there is hyperuricemia with bulky and/or advanced disease and/or high proliferative disease, in which case allopurinol should be added [12].

For the treatment of established TLS, the expert consensus panel recommended hydration with IV fluids at approximately 3 L/m² every 24 h to maintain a urine output of 80 to 100 mL/m²/h [12]. Diuretics may be considered in euvolemic patients to augment urine output, but they are contraindicated in patients with hypovolemia or obstructive uropathy. Alkalization with sodium bicarbonate must be individualized. The panel recommended treatment with rasburicase over allopurinol for patients with preexisting hyperuricemia (≥ 450 μmol/L or 7.5 mg/dL), with a dose of 0.15 to 0.2 mg/kg once daily in 50 mL of normal saline as an IV infusion over 30 minutes for 5 days [12]. Patients should be on a cardiac monitor with close follow-up of electrolyte levels. Hyperkalemia should be managed based on standard treatment. Asymptomatic patients with hypocalcemia require no treatment. Symptomatic patients may be treated with calcium gluconate 50 to 100 mg/kg IV, administered slowly. Hyperphosphatemia can be managed with adequate hydration and phosphate binders. For severe hyperphosphatemia, hemodialysis is preferred to peritoneal dialysis or continuous venovenous hemofiltration [12]. Hemodialysis is also indicated for persistent hypokalemia, hypocalcemia, hyperuricemia, or volume overload [12,13].

The rare incidence of spontaneous TLS in multiple myeloma makes timely diagnosis challenging. It can be missed if obscured by multisystem organ failure that can be explained by more common causes, such as the presence of acute decompensated heart failure or cardiogenic shock or renal failure.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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