When the Tumor Lyses: A Case Report on Spontaneous Tumor Lysis Syndrome

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Abstract
Tumor lysis syndrome (TLS) is an oncological emergency characterized by severe electrolyte disturbance that typically occurs when hematologic cancer patients have been started on systemic chemotherapy. We present an uncommon case of spontaneous TLS (STLS) occurring in a patient with cholangiocarcinoma. The patient was a 59-year-old male with newly diagnosed differentiated carcinoma of unknown origin who presented with weakness, fatigue, and light-headedness. Initial imaging revealed cholangiocarcinoma with innumerable pulmonary and hepatic metastases. The laboratory values showed leukocytosis, hypercalcemia, and lactic acidosis. He was diagnosed and treated for sepsis of pulmonary origin. Over the next 3 days, the patient’s clinical condition steadily worsened despite aggressive treatment, with new-onset hypoxic respiratory failure, acute kidney injury, and septic shock. Chemotherapy was administered, with new laboratory values showing hyperuricemia and hyperkalemia, consistent with STLS. The patient was transferred to the ICU and emergently started on dialysis but expired a day later from multi-organ failure. To our knowledge, this is the second case of STLS in cholangiocarcinoma. Our patient was unique in that he presented with hypercalcemia and normal phosphorus levels, instead of the typical hyperphosphatemia and secondary consumptive hypocalcemia. While the exact pathophysiology of STLS is still elusive, we believe that the patient’s initial sepsis-induced hypotension, aggressively enlarging tumor, and extent of metastasis all contributed to his rapid decline. Given the high mortality rate with TLS and its vague presentation, particularly in a chemotherapy-naïve solid tumor, a high level of clinical suspicion is needed to improve patients’ outcome.
Introduction

Tumor lysis syndrome (TLS) is an oncological emergency defined by hyperuricemia and hyperphosphatemia from massive tumor cell turnover. Complications from TLS may lead to multi-organ failure, seizures, and cardiac arrhythmias secondarily to electrolyte abnormalities. TLS is diagnosed via the Cairo-Bishop criteria (Table 1), and typically manifests as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Though commonly associated with hematological malignancies upon chemotherapy induction, it can occur spontaneously in solid tumors as well. It is estimated that mortality from spontaneous TLS (STLS) in a solid tumor is approximately 69% and has a worse prognosis than TLS from hematological malignancy [1]. Albeit rare, it is vital for early recognition of STLS and treatment to reduce morbidity and mortality.

We present the case of a patient with newly diagnosed cholangiocarcinoma who unfortunately suffered from STLS within 1 month of diagnosis, and ultimately passed away from multi-organ failure despite aggressive treatment.

Case Presentation

We report on a previously healthy 59-year-old male with newly diagnosed, poorly differentiated carcinoma of unclear origin with hepatic and pulmonary metastases who presented with weakness, fatigue, and lightheadedness.

The patient was in his normal state of health until 1 month prior to this admission, when he had started to develop postprandial right upper quadrant abdominal pain. At that time, the patient’s blood work revealed mild leukocytosis of 13,500/mm³ with neutrophilic dominance. Abdominal CT at the time revealed a large 11.7 × 6.1 cm right hepatic lobe mass with satellite lesions in the surrounding area, periportal and portacaval lymphadenopathy, and several pleura-based right lower lobe lung nodules (Fig. 1). Outpatient colonoscopy and endoscopy did not reveal any primary tumor. An ultrasound-guided liver biopsy had been performed a few days prior to his admission, which later demonstrated poorly differentiated carcinoma with nonspecific immunohistochemical staining.

On admission, the patient was tachycardic, tachypneic, and hypoxic on room air. His laboratory values were remarkable for hyponatremia, leukocytosis with neutrophilic dominance and left shift, hypercalcemia, and lactic acidosis. He also had new-onset transaminitis. A chest X-ray showed multiple bilateral pulmonary nodules, right basilar effusion, and consolidation. He was diagnosed with sepsis of pulmonary origin. Empiric vancomycin, cefepime, and levofloxacin were started, and normal saline rehydration was given for hypercalcemia. Oncology, pulmonology, and nephrology results were consulted.

Upon consultation, oncology recommended a staging workup including CT of the abdomen and pelvis, chest CTA, MRCP, and brain MRI. MRCP revealed enlargement of the hepatic mass, at the time measuring 14.6 × 14.0 cm, with imaging findings compatible with peripheral chol-
Angiocarcinoma (Fig. 2). Innumerable liver, lung, and peritoneal lesions consistent with metastatic disease were also found on CT. Brain MRI did not reveal any brain metastasis. The CA19-9 tumor marker was elevated to 151 U/mL. It was evident at this point that the tumor was highly aggressive in nature and had progressed significantly.

Over the following 2 days, the patient’s clinical condition continued to worsen despite empiric antibiotics and supportive therapies. His serum calcium remained elevated, and his lactic acidosis worsened. His infection workup remained negative, but the empiric antibiotics were continued given the neutrophilic leukocytosis. He also developed worsening hypoxic respiratory failure requiring intubation, septic shock requiring three pressor supports in the ICU, and acute kidney injury refractory to fluid resuscitation. IR placement of chemotherapy port was ordered in anticipation of emergent initiation of chemotherapy.

On the subsequent day, the patient developed hyperkalemia with worsening renal failure. Uric acid was elevated. The patient was diagnosed with STLS by clinical and laboratory
criteria and was given emergent hemodialysis and rasburicase. Patient's respiratory, renal, and hepatic function continued to deteriorate rapidly despite therapy (Table 2).

A family meeting was held the next day, and the family was informed of the patient's poor prognosis evidenced by multi-organ failure. The family understood that further intensive treatment was unlikely to return the patient to an acceptable quality of life and elected for the patient to receive comfort care only. Ventilatory and vasopressor support was withdrawn, and the patient passed away later that day.

### Discussion

We presented a 59-year-old male with metastatic cholangiocarcinoma who unfortunately deceased due to complications secondary to STLS. TLS is a complication that is more commonly associated with hematologic malignancy such as acute lymphocytic leukemia and Burkitt lymphoma upon initiation of chemotherapy. It is relatively rare for tumor lysis to occur spontaneously in solid tumors. However, it has been documented in gastrointestinal, renal, and uterine cancers. To our knowledge this is the second case presentation reporting TLS in cholangiocarcinoma [2].

Given the rapid progression of the disease, the patient passed away within 5 days of admission despite aggressive therapies. Unfortunately, no additional pathological evaluation could be done. Although the exact origin of the tumor remained elusive, based on radiographic characteristics, cholangiocarcinoma was the most likely primary origin of the tumor. On presentation, the patient was septic with evidence of multi-organ dysfunction. On day 4, the patient’s laboratory findings began to show hyperuricemia and hyperkalemia. Along with the patient’s new-onset renal failure, he met both the laboratory and the clinical criteria for TLS according to the Cairo-Bishop definition. It is important to note that, typically, TLS would cause hyperphosphatemia and secondary consumptive hypocalcemia from calcium phosphate precipitations. Interestingly, our patient presented with normal phosphate levels and
hypercalcemia. Our patient’s hypercalcemia could be explained by a lack of consumption, but it has also been described as a rare manifestation in cholangiocarcinoma both as a paraneoplastic syndrome and as a result of bone metastasis [3]. It is also known that hyperphosphatemia and hypocalcemia is less likely in STLS as compared to chemotherapy-induced TLS, due to the continued phosphate uptake into rapidly dividing tumor cells that would have been destroyed in typical TLS [4].

The exact mechanism of STLS remains elusive, with the leading theory suggesting that it is caused by rapid cell turnover. This could either be caused by the rapid growth of the tumor extending beyond its blood supply, or external factors facilitating cell death. Our patient presented with sepsis that subsequently developed into septic shock. As evidenced by the patient’s moderately elevated lactic acid level on admission, tissue hypoperfusion had been in place before his presentation. At this point, the electrolyte levels were largely normal, apart from hypercalcemia. As the patient’s sepsis progressed, his tissue perfusion decreased, evidenced by the worsening lactic acidosis. It is only then the patient developed acute kidney injury, hyperkalemic emergency, and hyperuricemia. It is possible that the rapidly progressing tumor could no longer be sustained by tissue hypoperfusion and global hypotension, eventually leading to high levels of tissue necrosis and thus STLS.

It is reasonable to assume that an enhanced systemic inflammatory response to infection in the setting of advanced metastatic disease may also play a role in increasing the risk for STLS. In a retrospective study it was suggested that a systemic inflammatory response with multi-organ dysfunction may be potentiated by STLS presumably through inflammatory cytokines and nitric oxide-mediated vasodilation [5]. However, in our case, evidence of systemic inflammatory response syndrome preceded the clinical finding of TLS.

**Conclusion**

We presented a unique case of STLS in a 59-year-old patient with metastatic cholangiocarcinoma. To our knowledge, this is the second case of STLS in cholangiocarcinoma. The mortality of STLS could be as high as 87.5% even in the setting of rasburicase use [1]. Given its uncommon occurrence and vague clinical picture, STLS may very likely be underdiagnosed, and a high degree of clinical suspicion is needed to ensure prompt intervention to change clinical outcomes.

**Statement of Ethics**

This case report complies with the ethical guidelines of COPE. The patient’s family have given their informed consent to publish this case and its associated pictures.

**Conflict of Interest Statement**

We have no conflict of interest to disclose. There was no financial involvement in the development of this manuscript.

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Author Contributions

M. Kundranda and N. Tanner were involved in the care of this patient. J. Dong and T. Cao drafted the case report. All authors were involved in the literature review and editing of the manuscript.

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