

Case report

Tumor lysis syndrome in advanced and high-grade endometrial cancers: A case report and review of the literature

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1. Introduction

Tumor lysis syndrome (TLS) is an emergency in which the destruction of tumor cells and release of intracellular contents leads to electrolyte abnormalities that can precipitate acute renal failure, heart failure and arrhythmias, seizures, and sudden death (Cairo & Bishop, 2004). While TLS is most common in patients with hematologic malignancies following chemotherapy initiation, TLS has been reported in patients with endometrial carcinoma, leiomyosarcoma, and endometrioid stromal sarcoma (Ahmed et al., 2019), with most cases resulting in rapid death, especially in women with high grade disease. There is some evidence indicating that high grade endometrial carcinoma portends a particularly poor prognosis if complicated by TLS (Table 1). Here we report on two additional cases of high-grade endometrial carcinoma diagnosed with TLS, one treatment related and the other spontaneous.

2. Patient 1

A 61-year-old presented with rapidly progressive abdominal distension and vaginal bleeding. A bedside abdominal ultrasound demonstrated a large pelvic mass. Serum CA-125 was significantly elevated; pertinent laboratory findings are presented in Table 2. Computed tomography (CT) demonstrated a bilateral pulmonary emboli (PE), a complex pelvic mass, diffuse peritoneal carcinomatosis, small- to moderate-volume ascites, and abdominopelvic lymphadenopathy (Fig. 1). Pelvic ultrasound demonstrated heterogeneous uterine echotexture, 23-mm endometrial echo complex, hypoechoic lower uterine segment mass, and large complex adnexal structures bilaterally.

Paracentesis cytology demonstrated metastatic high-grade carcinoma of Mullerian origin. Pelvic exam was significant for necrotic tissue extruding from the cervical os. Pathology resulted with Pap smear, endocervical curettage, and vacuum-assisted endometrial biopsies all consistent with carcinosarcoma showing a major component (90%) of high-grade serous carcinoma and minor component (10%) of high-grade sarcoma. She demonstrated no respiratory distress at time of presentation.

Three days following discharge on oral rivaroxaban, she was seen by Gynecologic Oncology. At that time, outpatient chemotherapy was planned. Five days later, the patient presented to the emergency department with worsening dyspnea and abdominal pain and was admitted for expedited neoadjuvant chemotherapy. On hospital day #2, she received carboplatin AUC 5 and paclitaxel 175 mg/m²; creatinine at time of administration was 0.6 mg/dL. Her condition remained unchanged until day #4 when she endorsed worsening dyspnea and abdominal pressure with desaturation requiring 4L oxygen. Creatinine and urine output worsened without response to crystalloid and albumin boluses. Serial chemistry demonstrated worsening hyperkalemia, hyperphosphatemia, and hypocalcemia. Serial chest X-rays demonstrated significant bibasilar atelectasis, likely secondary to malignant ascites. On day #5, she became severely hypoxemic with desaturations on 6L oxygen, thus requiring intubation and transfer to the intensive care unit (ICU).

The hypercreatinemia, hyperkalemia, hyperphosphatemia, and hypocalcemia continued to worsen. Uric acid was noted to be 10.8 mg/dL. The patient thus met criteria for TLS, and rasburicase (0.2 mg/kg) was administered until complete normalization of uric acid levels after 3

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Table 1
Review of tumor lysis syndrome cases diagnosed in advanced and/or high-grade endometrial adenocarcinoma.

First Author, Year*	Histology	Stage	TLS characterization	Outcome
Ahmed, 2019	Undifferentiated endometrial carcinoma	IVB	Post treatment	Death due to TLS
Alaigh, 2017	Uterine leiomyosarcoma	IVB	Spontaneous	Death due to TLS
Berger, 2017	G1 endometrial adenocarcinoma	IVB	Spontaneous	Alive with disease
Berger, 2017	Uterine serous	IVB	Spontaneous	Death due to treatment related events
Chango Azanza, 2020	Endometrial adenocarcinoma w neuroendocrine features	At least IIIC2	Spontaneous	Death due to TLS
Godoy, 2010	High grade endometrial carcinoma	Recurrent metastatic	Post treatment	Death due to TLS
Harada, 2017	Dedifferentiated endometrial carcinoma	IVB	Spontaneous	Death due to TLS
Hiraizumi, 2011	Uterine leiomyosarcoma	IVB	Post treatment	Death due to malignancy
Ito, 2018	Uterine serous	IIIC2	Post treatment	Death due to TLS
Pabon, 2018	LMS	Recurrent with bulky metastasis	Post treatment	Death due to TLS
Zhao (current)	Carcinosarcoma	IVB	Post treatment	NED
Zhao (current)	G3 endometrial adenocarcinoma	IVB	Spontaneous	Death due to TLS

* References for articles included in the table can be found in [Appendix A](#).

days. There was concern for abdominal compartment syndrome given her anuria, worsening hypercreatinemia, and bladder pressure of 30 mmHg. Thus, paracentesis and a peritoneal drain placement were performed, improving bladder pressures and urine output. She was weaned off mechanical ventilation following these procedures. However, creatinine and phosphate continued to uptrend, and potassium remained elevated, suspicious for ongoing TLS. A sharp decrease in repeat serum CA-125 suggested robust chemotherapy response, consistent with potential rapid tumor necrosis. Hemodialysis was ultimately performed twice with subsequent improvement in hyperkalemia, hypercreatinemia, and hyperphosphatemia. Notably, throughout this patient's time in the ICU multiple consultants recommended withdrawal of care and were reticent to offer services such as dialysis due to concerns regarding futility.

Aside from transient filgrastim-responsive leukopenia, the patient's laboratory values, urine output, and oxygen saturation on room air improved, and she was transferred from the ICU to the floor, where her electrolyte abnormalities continued to resolve. A second cycle of chemotherapy was administered; paclitaxel dosing was changed to

Table 2
Notable lab values diagnostic for TLS for Patients 1 and 2 at time of presentation.*

Patient	Potassium (mEq/L)	Creatinine (mg/dL)	Uric Acid (mg/dL)	Phosphorus (mg/dL)	Calcium (mg/dL)	CA 125 (U/mL)
1	6.1	3.03**	10.8	5.4	7.1	423
2	5.7	2.5***	9.0	4.8	6	67

* Lab values consistent with TLS are highlighted in bold. These patients both met criteria for laboratory and clinical TLS.

** Baseline 0.6.

*** Baseline 1.5.

weekly dose-dense (80 mg/m²) for cycle 2–6. Serum chemistry was closely monitored following infusion and remained within normal limits. She was deemed stable for discharge with normal serum labs including a creatinine that had normalized to <0.7 mg/dL.

The patient underwent a third cycle of neoadjuvant chemotherapy as an outpatient without complication. Repeat serum CA-125 was significantly reduced from prior. Repeat CT-A/P demonstrated reductions in uterine mass size, ascitic volume, and peritoneal nodularity. Given evidence of robust chemotherapy response, she underwent complete interval tumor reductive surgery comprising hysterectomy, bilateral salpingo-oophorectomy, omentectomy, removal of nodular cystic implants, and argon beam coagulation. Surgical pathology of the bilateral adnexae demonstrated focal metastatic uterine serous carcinoma with background of post-chemotherapy necrosis. Surgical pathology of the uterus, cervix, and cystic implants were all consistent with post-chemotherapy necrosis, indicating that almost no viable tumor remained after 3 cycles of chemotherapy. The patient tolerated the procedure well and was discharged.

Following interval debulking she received 3 uneventful cycles of carboplatin AUC 5 and weekly paclitaxel. Eighteen months following completion of primary therapy, serum CA-125 was 6 U/mL, and repeat CT-A/P demonstrated no evidence of recurrent disease.

3. Patient 2

A 75-year-old presented with lower extremity edema, vaginal bleeding and foul smelling discharge. Her medical comorbidities consisted of diabetes mellitus, chronic kidney disease, and hypertension. Imaging revealed extensive tumor burden including an enlarged heterogeneous uterus with central fluid and gas, bulky thoracic and abdominal pelvic lymphatic disease, multiple pulmonary nodules and multiple intraparenchymal hepatic metastases. Serum labs revealed multiple abnormalities including hyponatremia, hyperphosphatemia, hypocalcemia, elevated uric acid, and creatinine notably elevated above baseline (Table 2). Leukocytosis was also present. Uric acid was found to be 9.0 mg/dL. Rasburicase was administered when it was noted that she met Cairo-Bishop criteria for TLS. Broad-spectrum antibiotics were administered and electrolyte abnormalities were managed in a step-down unit. An endometrial biopsy obtained at time of admission resulted with G3 endometrial adenocarcinoma. Inpatient chemotherapy was considered; however, her status continued to decline despite aggressive resuscitative measures. She and her family were counseled regarding poor prognosis over the course of the admission and had elected to make her DNR/DNI. She was transferred to hospice on hospital day 9.

4. Discussion

In 2004 Cairo and Bishop proposed laboratory and clinical criteria—hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, hypercreatinemia, cardiac arrhythmia or sudden death and seizure—to aid in the diagnosis of TLS (Cairo and Bishop, 2004). While other definitions exist, the Cairo-Bishop criteria are the most commonly used in clinical practice.

This report is the first to document a case of TLS in a patient with uterine carcinosarcoma, and the only reported case of advanced high-grade endometrial malignancy diagnosed with TLS that survived. In

this case, factors that led to patient survival included rapid recognition of a rare condition, immediate administration of rasburicase until normalization of uric acid values, and the willingness to use extreme measures including mechanical ventilation and dialysis in a clinical scenario that was seen by some involved providers as hopeless.

TLS in solid tumors carries high mortality risk, with one study reporting an inpatient mortality rate of 47% (Caravaca-Fontán et al.,

2017). Mortality from TLS in endometrial carcinoma appears to be similarly high based on a review of the currently published literature on the subject (Ahmed et al., 2019; Castellano et al., 2019). Prior to this report, there have been ten cases of TLS diagnosed in endometrial cancer with most of them succumbing rapidly to the sequelae of disease. When looking at all cases of TLS in endometrial cancer, including those in this report, the mortality rate is at least as high as that reported in the general

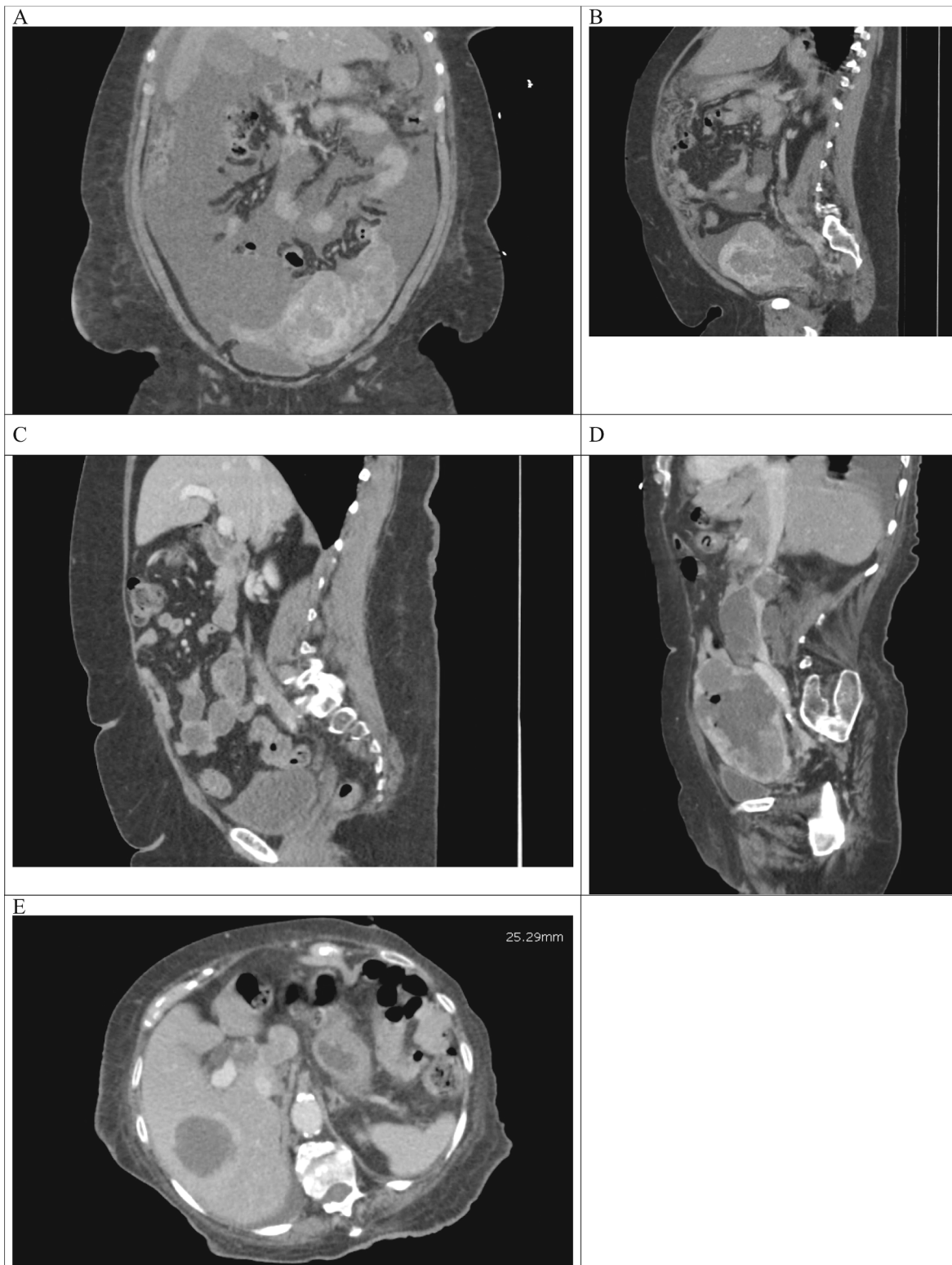


Fig. 1. CT images from Patient 1 and 2.

literature (Table 1). While there is surely a component of publication bias within this limited data, there is a suggestion of a trend towards severe and life-threatening TLS within the population of women diagnosed with advanced high-grade endometrial cancer. Based on this, it is recommended that a particularly high index of suspicion be maintained in women presenting with high-risk features.

In both solid and nonsolid tumors, factors such as large tumor burden, rapid proliferation, metastasis, elevated serum lactate dehydrogenase (LDH), chemosensitivity, and preexisting renal disease are associated with increased risk of TLS (Cairo & Bishop, 2004; Mirrakhimov et al., 2014). Furthermore, risk of TLS increases in settings of pre-existing hyperuricemia, hyperphosphatemia, and hyperkalemia.

Optimal management of TLS is prevention following risk stratification. Prophylaxis for patients at intermediate- and high-risk of developing TLS involves IV hydration to maintain a high urine output (>2.5L/day) and a hypouricemic agent (oral or IV allopurinol or IV rasburicase); monitoring for development of TLS and its sequelae is recommended regardless of level of risk (Cairo et al., 2010). Treatment of established TLS involves preservation of renal function, reduction of serum uric acid levels, and management of specific electrolyte abnormalities and their sequelae. Dialysis is indicated in the settings of severe oliguria or anuria, persistent hyperkalemia, hyperphosphatemia-induced symptomatic hypocalcemia, and intractable fluid overload when other treatment measures have failed. While these align with standard dialysis indications for AKI, the threshold to dialyze in TLS is generally lower due to risk of rapid-onset severe hyperkalemia with TLS-induced AKI (Howard et al., 2011).

Although endometrial cancer complicated by TLS is uncommon, there is some evidence supporting particularly high morbidity and mortality risk in high-grade histologies. Gynecologic oncologists must employ heightened clinical suspicion and be prepared to risk-stratify, diagnose, and initiate prophylaxis or treatment in patients when indicated.

5. Statement of consent

Written informed consent was obtained from the Patient 1 for publication of this case report and accompanying images. Patient 2 was expired and her family was not able to be reached for informed consent despite multiple attempts. A copy of the written consent is available

upon review by the Editor in Chief of the journal upon request. This study was approved by the University of Southern California IRB.

Author contributions

J Zhao – manuscript author.
H Miller – editing, IRB submission.
E Blake – concept, editing, manuscript finalization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2021.100761>.

References

- Ahmed, Z., Barefah, A., Wasi, P., Jones, G., Ramsay, J., 2019. Tumour lysis syndrome in a patient with undifferentiated endometrial stromal sarcoma. *Gynecol. Oncol. Rep.* 28, 41–43. <https://doi.org/10.1016/j.gore.2019.02.006>.
- Cairo, Mitchell S., Coiffier, B., Reiter, A., Younes, A., TLS Expert Panel, 2010. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: An expert TLS panel consensus. *Br. J. Haematol.* 149 (4), 578–586. <https://doi.org/10.1111/j.1365-2141.2010.08143.x>.
- Cairo, M.S., Bishop, M., 2004. Tumour lysis syndrome: New therapeutic strategies and classification. *Br. J. Haematol.* 127 (1), 3–11. <https://doi.org/10.1111/j.1365-2141.2004.05094.x>.
- Caravaca-Fontán, F., Martínez-Sáez, O., Pampa-Saico, S., Olmedo, M.E., Gomis, A., Garrido, P., 2017. Tumor lysis syndrome in solid tumors: Clinical characteristics and prognosis. *Med. Clin.* 148 (3), 121–124. <https://doi.org/10.1016/j.medcli.2016.10.040>.
- Castellano, T., Bulard, B.A., Staley, A., Moore, K.N., 2019. Tumor lysis syndrome in gynecologic cancers: An uncommon but important diagnosis to recognize. *Gynecol. Oncol. Rep.* 30, 100514. <https://doi.org/10.1016/j.gore.2019.100514>.
- Howard, S.C., Jones, D.P., Pui, C.-H., 2011. The tumor lysis syndrome. *N. Engl. J. Med.* 364 (19), 1844–1854. <https://doi.org/10.1056/NEJMra0904569>.
- Mirrakhimov, A.E., Ali, A.M., Khan, M., Barbaryan, A., 2014. Tumor lysis syndrome in solid tumors: An up to date review of the literature. *Rare Tumors.* <https://doi.org/10.4081/rt.2014.5389>.