Review article

Tumor lysis syndrome in gynecologic cancers: An uncommon but important diagnosis to recognize

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A B S T R A C T

Objectives: To describe the incidence, treatment and outcomes associated with tumor lysis syndrome (TLS) in women with gynecologic cancer (GOC).
Methods: A retrospective multi-institutional review of TLS associated with GOC. Women presenting with an elevated serum uric acid managed with intravenous (IV) rasburicase were included. Descriptive statistics of patient demographics, clinical findings, and outcome data was completed.
Results: From two large academic institutions N = 18 patients were found to meet inclusion criteria from 2008 to 2018, reflecting an approximate 5% incidence of clinically treated TLS associated with GOC in our cohort. Median age was 60 years, a majority were Caucasian (n = 11, 61.1%), median BMI was 36.2. TLS was associated with a high-grade GOC in n = 17 (94.4%) cases. TLS was commonly diagnosed with a new GOC (n = 12, 70.6%) and following receipt of chemotherapy in n = 9 (50.0%) cases. Six (66.7%) patients were treated with paclitaxel or combination, five (55.5%) with a platinum or combination, and two (22.2%) with a CD47 inhibitor. Chief complaints included electrolyte and renal abnormalities (n = 11, 73.3%). Peak serum uric acid, potassium, creatinine and phosphorus levels were 14.1 mg/dL, 5.7 mEq/L, 5.1 mg/dL, and 6.8 mg/dL, respectively. Nine patients received hospice during their admission with 3 (20%) deaths occurring as inpatients. There were 12 deaths with median OS of 16 d (range: 2–87 d).
Conclusions: Though rare, TLS can be associated with GOC. Early recognition of presenting symptoms, laboratory findings and expedited treatment may help with electrolyte recovery; however, TLS associated with GOC may herald a rapidly deteriorating state with significant associated mortality.

1. Introduction

Tumor lysis syndrome (TLS) is a condition marked by a constellation of electrolyte abnormalities usually occurring in the setting of highly proliferative hematologic malignancies. TLS can occur spontaneously, but is typically associated with initiation of cytotoxic chemotherapy. As toxic intracellular ions, nucleic acids and cell metabolites are released within the bloodstream major electrolyte abnormalities ensue, including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Shifts in the extracellular ion content results in serious downstream effects including acid/base anomalies, obstructive uropathy and acute renal failure, cardiac abnormalities/ arrhythmias, seizures and ultimately death. The increased breakdown of purine nucleotides into uric acid results in a high serum concentration of uric acid, which is the defining derangement of TLS (Cairo and Bishop, 2004). As uric acid precipitates in the acidic environment of the

renal tubules, an obstructive uric acid nephropathy develops which can manifest as oliguria and acute kidney injury (AKI). Hyperphosphatemia can develop as malignant cells have upwards of four times the intracellular phosphate concentration compared to a normal cell (Cairo and Bishop, 2004). Furthermore, phosphate precipitates with calcium in the renal tubules leading to hypocalcemia and further obstruction (Cairo and Bishop, 2004). As renal function declines, metabolic acidosis develops, accelerating the risk for severe arrhythmia, seizure, and death. Thus, prompt recognition, diagnosis and treatment is warranted.

The Cairo-Bishop criteria provides a framework in which both clinical and laboratory findings are required to diagnose clinical TLS [Table 1]. Once diagnosed, TLS should be urgently managed in a multidisciplinary approach including nephrology, clinical pharmacy, and medical oncology, if available. Adequate hydration should be initiated; however, caution in the case of oligo and anuria should be taken. Equal fluid intake to urinary output should be attempted, and diuretics should

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Table 1

Cairo-Bishop criteria for diagnosis of TLS.

Laboratory finding*	Serum concentration	Change from baseline	Clinical finding**
Uric acid	≥ 8 mg/dL	Increase 25%	Serum creatinine ≥ 1.5 × ULN
Potassium	≥ 6 mmol/L	Increase 25%	Cardiac arrhythmia/sudden death
Phosphorous	≥ 4.5 mg/dL	Increase 25%	Seizure
Calcium	≤ 7 mmol/L	Decrease 25%	

* Laboratory TLS is defined by any 2 of 4 findings.

** Clinical TLS diagnosis requires any clinical finding in the setting of laboratory TLS.

be avoided if obstructive uropathy is suspected (Coiffier et al., 2008). Alkalization is no longer recommended in the acute treatment of TLS as it may increase the risk of calcium phosphate crystal precipitation. This treatment should be reserved for patients with metabolic acidosis and under the direction of nephrology (Coiffier et al., 2008).

Acute management of TLS includes addressing each electrolyte derangement and the associated clinical sequelae. Hyperphosphatemia can lead to nausea, vomiting, and lethargy. Hyperphosphatemia can initially be treated with hydration and phosphate binders, such as aluminum hydroxide (Coiffier et al., 2008). Asymptomatic hyperkalemia can be addressed with sodium polystyrene orally or rectally. Symptomatic patients require immediate interventions, such as intravenous (IV) insulin (0.1U/kg) with a 25% dextrose bolus of 2 ml/kg^2. Elevated potassium levels greater than 7.5 mEq/L or an electrocardiogram (EKG) demonstrating widened QRS complexes requires immediate intervention with continuous cardiac monitoring. Lastly, symptomatic hypocalcemia can result in muscle cramps, which can be treated with calcium gluconate 50–100 mg/kg IV; however, the provider must note this may precipitate further obstructive uropathy (Coiffier et al., 2008). Dialysis use in TLS has decreased with the increasing use of rasburicase, but involvement of a nephrology specialist should be employed early in the clinical course.

For acute clinical TLS, pharmacologic management is key and best if planned in conjunction with a clinical pharmacist or as per hospital policy. The optimal choice for managing acute TLS is the use of recombinant *urate oxidase*, rasburicase, and this drug should be considered for initial management of TLS and hyperuricemia. The US Food and Drug Administration (USDA) dosing guidelines recommend 0.2 mg/kg for up to 5 days (Elitek, 2015) and fixed dose rasburicase are limited to inpatient use only, with careful and frequent uric acid and clinical monitoring (Elitek, 2015). In a large trial of 100 patient with aggressive non-Hodgkin's lymphomas, uric acid levels were found to decrease significantly within 4 h of administration of rasburicase and normalize for all patients receiving at least 3 days of treatment (Coiffier et al., 2003). Known G6PD deficiency is the primary contraindication to rasburicase administration. Another frequently encountered medication used in conjunction with TLS is allopurinol. Allopurinol is a competitive inhibitor of *xanthine oxidase,* preventing the metabolism of xanthine to uric acid, thus, only preventing uric acid formation. This is best used prior to cytotoxic therapy in those with high-intermediate risk of developing clinical TLS (Cairo and Bishop, 2004).

TLS has not been comprehensively described in gynecologic cancers (Hiraizumi et al., 2011; Weed et al., 2003; Godoy et al., 2010; Yahata et al., 2006; Baeksgaard and Sorensen, 2003; Okamoto et al., 2015; Berger et al., 2017; Alaigh and Datta, 2017; Shukla et al., 2017; VanHise et al., 2017). Data for solid malignancies rely on case reports. A 2014 review reported that among all solid tumors, TLS was most commonly reported in lung cancers (21 cases). Followed by breast (13 cases), then gynecologic cancers (10 cases) (Mirrakhimov et al., 2014). Table 2 demonstrates the most recent 13 reported cases of TLS associated with a gynecologic malignancy (Hiraizumi et al., 2011; Chan et al., 2005; Camarata et al., 2013; Godoy et al., 2010; Yahata et al., 2006; Baeksgaard and Sorensen, 2003; Okamoto et al., 2015; Berger et al., 2017; Alaigh and Datta, 2017; Shukla et al., 2017; VanHise et al., 2017). TLS was most commonly associated with ovarian or uterine

cancers and occurred at the time of new diagnosis or recurrence [Table 2].

Despite the paucity of clinical case reporting, risk stratification and identification of those at risk for developing TLS in solid cancers is becoming increasingly utilized. Thus, the incidence of clinical TLS associated with solid tumors has been found to be as a great as 1 in 5 cases (Durani et al., 2017). Currently, according to Cairo-Bishop criteria, all solid tumors are considered low risk for TLS (Cairo et al., 2010). Factors that increase the risk for developing TLS include high chemo-sensitivity, a highly metabolic and rapidly proliferating malignancy, high tumor burden, and patients with known renal dysfunction or dehydration (Mirrakhimov et al., 2014; Cairo et al., 2010). Due to the relative lack of reported information for this treatable oncologic emergency, we sought describe the incidence, clinical presentation, usual management course and outcomes associated with TLS in gynecologic malignancies.

2. Methods

A multi-site IRB approved retrospective study from two academic sites was performed. Patients from the University of Oklahoma (OU) and University of North Carolina (UNC) were included, offering a differing social, racial/ethnic and economic population for review. Women with a new diagnosis or established diagnosis of a gynecologic malignancy admitted to the hospital with a new serum uric acidemia and managed with IV rasburicase were included. At OU, all inpatients receiving IV rasburicase were eligible, and patient records were collected by a query of the inpatient pharmacy records from the years of 2008–2018. All patients were screened and those meeting eligibility criteria were selected. At UNC, the electronic medical records (EMR) was queried by the North Carolina Tracks (NCTracks) data informatics group. All women meeting criteria were identified. Baseline patient demographics, cancer diagnosis and treatment, hospital admission information, laboratory, TLS treatment and outcome data were collected. Descriptive analysis and summary statistics of patient characteristics, clinical factors, laboratory findings, treatment and outcome data was performed.

3. Results

From OU, pharmacy records identified 1134 inpatients from 2008 to 2018 receiving at least one inpatient dose of IV rasburicase. Following screening for inclusion criteria, 344 (30.3%) were women and of those 307 (89.2%) women had a known malignancy. Furthermore, fifteen (4.9%) of those women had a new or established malignancy of gynecologic origin. From UNC, three additional patients with TLS in the setting of gynecologic malignancy were identified from 2014 to 2018. Thus, a total of N = 18 patients met inclusion criteria.

The baseline characteristics (see Table 3) for our cohort showed median age was 60 years (range: 35–71 y), majority Caucasian (n = 11, 61.1%), and median BMI 36.2. Ovarian cancer was the most common gynecologic cancer site associated with TLS (n = 8, 44.4%), followed by uterine malignancies (n = 6, 33.3%), and 1 cervical malignancy (5.6%). The remaining 3 malignancies were of an undifferentiated gynecologic origin (16.7%). TLS was nearly always associated with a

Table 2
Overview of reported gynecologic malignancies complicated by TLS.

Year	Age	Site	Histology	Stage	Associated Treatment	Days following Treatment	Result	Citation
1992	66	Vulva	Squamous Cell		Cisplatin 5-flourouracil	3–5	Resolution	*Baeksgaard*
1994	47	Ovary	Serous		Carboplatin Cyclophosphamide	2	Resolution	*Baeksgaard*
1998	74	Vulva	Squamous Cell		Cisplatin 5-flourouracil	9	Death	*Baeksgaard*
2005	62	Ovary	High grade serous	Progressive Platinum-resistant IIIC	Topotecan	14	Hydration Allopurinol Death	*Chan*
2006	53	Ovary	Clear cell	Recurrent IC	Carboplatin Paclitaxel	5	Hydration Alkalization Resolution	*Yahata*
2010	60	Uterine	Endometrial	Recurrent IIB	Carboplatin Paclitaxel	4	Dialysis Death	*Godoy*
2011	36	Uterine	Epitheliod LMS	New Diagnosis IV	Vincristine Actinomycin-D Cyclophosphamide	7	Dialysis Resolution	*Hiraizumi*
2012	63	Ovary	High grade serous	Recurrent metastatic IIC	Carboplatin Paclitaxel	2	ICU Death	*Camarata*
2015	62	Ovarian	Endometrioid	New Diagnosis IC	None		ICU Surgery Resolution	*Okamoto*
2017	33	Uterine	Endometrioid	New Diagnosis IVB	None		Surgery Resolution	*Berger*
2017	58	Uterine	LMS	New Diagnosis IVB	None		ICU Rasburicase Death	*Alaigh*
2017	40	Ovary	Endodermal Sinus Tumor	IVB	Palliative radiation	*Not stated*	Hydration Allopurinol BEP treatment Death	*VanHise*
2017	49	Ovary	Adeno-carcinoma	New Diagnosis IVB	None		Rasburicase Resolution Chemotherapy	*Shukla*

LMS: Leiomyosarcoma BEP: Bleomycin, Etoposide and Cisplatin.

Table 3
Patient clinical characteristics and outcomes.

Clinical characteristic	N = 18
Age (median)	60 years
BMI (median)	36.2
Race/Ethnicity	White/Caucasian, n = 11
Missing 1	Black/African American, n = 2
	Asian/Middle Eastern, n = 1
	Hispanic/American Indian/Pacific Islander, n = 3
Cancer site	Uterine, n = 6,
	Ovarian, n = 8,
	Cervical, n = 1,
	Un- or De-differentiated, n = 3
Stage	III, n = 6
Missing 2	IV, n = 10
Grade	High/grade3, n = 17
	Low/grade1, n = 1
Disease status	New Dx, n = 12
	New Recurrence, n = 6
Treatment	Platinum containing, n = 5
n = 9	Taxol containing, n = 6
	Bevacizumab, n = 1
	Anti-CD47, n = 2
Presenting serum labs (mean)	Creatinine 4.1 mg/dL
	Potassium 5.2 mEq/L
	Uric Acid 14.1 mg/dL
	Calcium 8.0 mg/dL
	Phosphate 6.1 mg/dL
Outcome	Dead, n = 12
Missing1	Alive not treating, n = 2
	Alive and treating, n = 3

high-grade gynecologic malignancy (n = 17, 94%), with only one case associated with a low-grade ovarian malignancy.

TLS was diagnosed at the time of cancer diagnosis in most cases (n = 12, 70.6%), while the remainder were made at the time of recurrence of a previously known gynecologic malignancy. TLS was diagnosed following administration of chemotherapy in n = 9 (50.0%) cases with a median 14-day interval between treatment and TLS diagnosis. Of those who received treatment, six (66.7%) were treated with paclitaxel or paclitaxel combination, and five (55.5%) were treated with a platinum or platinum combination. Only one of the 9 (11.1%) was receiving bevacizumab. Two of these nine cases (22.2%) were treated with a CD47 inhibitor. One case was associated with major surgery. None of the cases were associated with radiation therapy.

The admitting diagnosis and/or chief complaint was provided in 15 of the 18 cases. Electrolyte and renal abnormalities were the most common diagnoses on admission (n = 11, 73.3%). Acute renal failure (ARF) was reported in 7 cases (46.7%); hyperkalemia in 5 cases (33.3%); shortness of breath (SOB) in 4 cases (26.7%); and, nausea/vomiting in 3 cases (20.0%). Upon admission, 13 (72.2%) were admitted to the general oncology ward, 3 (16.7%) admitted to the intensive care unit (ICU) and 2 (11.1%) were admitted to an intermediate care or "step down" hospital bed. Nephrology consultation was pursued in 17 (94.4%) cases, typically within one hospital day. On average, 2 (range: 1–12) doses of rasburicase were given by hospital day 2, with a median 9-day (range: 4-16d) admission. A median of 2 doses (range 1–18 doses) of allopurinol was administered in 7 (38.9%) cases.

The mean primary serum uric acid, potassium, creatinine, and phosphorus levels were 14.1 mg/dL (normal female range 2.4–6.0 mg/dL), 5.2 mEq/L (normal range 3.5–5.5 mEq/L), 4.1 mg/dL (normal range 0.6–1.2 mg/dL), and 6.1 mg/dL (normal range 2.4–4.5 mg/dL), respectively. The mean corrected serum calcium nadir was 8.0 mg/dL

([Table 2](#)). Initially, reported uric acid levels remained equivalent to peak serum uric acid level (14.1 mg/dL) during hospital admission. In contrast, serum potassium, creatinine and phosphorus levels demonstrated a rise to 5.7 mEq/L, 5.1 mg/dL, and 6.8 mg/dL, respectively, following initial levels. Corrected serum calcium levels also declined to 7.1 mg/dL following initial levels.

Full laboratory recovery, defined as normalization of serum uric acid, potassium and creatinine, occurred in 8 (44.4%) cases. For the complete cohort, there were 12 deaths with median OS of 16 d (range: 2–87 d) following diagnosis of TLS. Ten patients received additional chemotherapy following diagnosis and treatment of TLS. Of these ten patients, 2 (20%) died within 1 month of retreatment, while 5 (50%) are still alive at the time of this study. Three women (30%) are still being treated treating. Median follow up time is 29 d (range: 2–321 d). Nine (50.0%) patients with TLS were placed on hospice during their index admission with 3 (30%) of those deaths occurring as inpatients. None of the deaths occurred while in the ICU.

4. Conclusions

TLS associated with gynecologic malignancies remains rare. As with hematologic malignancies, our study finds that a majority of cases are associated with new diagnosis and can be precipitated by cytotoxic therapies. However, there are increasing reports of TLS associated with more indolent hematologic malignancies, such as chronic lymphocytic leukemia (CLL). This association may be due to increasing use of newer biologic and targeted agents like anti-CD20 and Rituximab (Cheson et al., 2017). Rituximab and other anti-CD20 monoclonal antibodies have been used in combination with anti-CD47, which are investigational drugs used in ovarian cancers (Advani et al., 2018). To our knowledge, we report the first cases of TLS associated with anti-CD47 in GOC. Anti-CD47 is a monoclonal antibody against the CD47 ligand involved in the signal regulatory protein alpha (SIRP α) pathway. It is highly expressed on a variety of cancer cells, serving as an immune cell checkpoint against macrophage-mediated phagocytosis (Weiskopf, 2017). Thus, as we expand the armamentarium for treating GOC, familiarity with the known side effects of novel and investigational treatments, including TLS, is required.

In gynecologic malignancies, the majority of the patients who present with TLS, electrolyte and renal dysfunction as well as resultant fluid retention and acute kidney injury are the typical primary presenting diagnoses. Unfortunately, this is a common presentation for women with large pelvic masses and suspected new GOC. Urine analysis, such as a fractional excretion of urine sodium (FENA), may be consistent with an obstructive etiology. Because the obstruction is within the renal tubules, standard diverting measures are unhelpful. In fact, from our series, three patient underwent ureteral assessment and bypass with 2 stent placements and 1 percutaneous nephrostomy tube placement. All three presented with AKI. Therefore, the diagnosis of TLS may be obfuscated and/or worsened by the presence of true mechanical post-renal obstruction.

For this series of patients, the initial serum uric acid level was equal to the peak serum uric acid level, whereas other electrolytes worsened following admission. This indicates that once suspicion is high and uric acid levels are elevated, rapid and effective treatment must be pursued. Due to the requisite use of rasburicase for inclusion into this study, we do not have information on the clinical course of patients who were not treated with this drug.

Of the 8 patients who experienced adequate renal and electrolyte recovery, all were diagnosed and treated for TLS by hospital day 4. The majority were diagnosed and treated by hospital day 2. Conversely, those who did not experience recovery of electrolyte or renal function were diagnosed and treated after hospital day 4. While the sample size is too small to test for significant differences, this highlights the potential importance of prompt clinical recognition and action for improved clinical outcomes.

Less than a third of all patients and only half of those experiencing electrolyte and renal recovery were able to successfully resume cancer treatment. Even for those in who achieved electrolyte and renal recovery and/or resumed cancer treatment, the median OS was < 4 months. Thus, for patients who do not achieve prompt recovery despite adequate treatment, the involvement of palliative care and end-of-life (EOL) services should be obtained. We suggest that for all women with TLS, a goals of care discussion is warranted due to the high associated mortality rate. In our series, 9 (50%) of our patients were referred to hospice services during their index admission and a large majority (n = 6, 67.7%) of those were able to be discharged for an out of hospital death. Our data suggest that despite aggressive interventions, the overall prognosis is poor with an associated mortality of 72% and median OS of just over two weeks. While uncommon, gynecologic oncologists should be familiar with the presenting symptoms, diagnostic criteria and appropriate management of TLS as well as the associated morbidity and mortality of this rare syndrome in GOC.

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CRediT authorship contribution statement

T. Castellano: Conceptualization, Investigation, Data curation, Methodology, Writing - original draft. **B.A. Bulard:** Investigation, Data curation, Writing - review & editing. **A. Staley:** Investigation, Data curation, Writing - review & editing. **K.N. Moore:** Writing - review & editing, Supervision.

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