Case Report

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Acute Tumor Lysis Syndrome after Cisplatin and Gemcitabine for Treatment of Urothelial Carcinoma of the Renal Pelvis: Case Report and Review of Literature

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Abstract

Tumor lysis syndrome (TLS) is a potentially fatal complication of oncological therapy. It is rarely described in patients with solid tumors, even rare in urological cancer. To the best of our knowledge, there were only two cases describing TLS following chemotherapy for metastatic urothelial carcinoma documented in the literature, although only one occurred after gemcitabine, another case occurred after PD-1 Immunotherapy. Case presentation: We present the case of a 67-year-old female who developed acute renal failure and tumor lysis syndrome after a single infusion of cisplatin and gemcitabine for metastatic renal pelvic urothelial carcinoma. Conclusions: Patients with urothelial carcinoma that are highly proliferative and have high tumor burden are at high risk of developing hyperuricemia and TLS, while undergoing chemotherapy. Although TLS is rare in solid tumor, oncologists should be alert when treating patients at high risk of TLS, and determine appropriate prophylaxis. We also proposed biomarker based risk stratification for patients with high risk for TLS.

Keywords: Tumor lysis syndrome (TLS); Liver metastasis; Oncologic emergency; Urothelial carcinoma of the renal pelvis cisplatin; Gemcitabine; Rasburicase

Introduction

Acute tumor lysis syndrome (TLS) is considered an oncologic emergency which may result in significant morbidity and mortality in cancer patients [1-3]. It results from rapid lysis of tumor cells and release of intracellular contents such as potassium, phosphorus and uric acid. Patients with ATLS commonly present with cardiac arrhythmias, seizures, muscle cramps, acute kidney injury (AKI), and vomiting [2]. TLS is most commonly seen in cases of hematologic malignancies such as Burkitt lymphoma and leukemia; however, cases of TLS have been reported in patients with rapidly growing, bulky, therapy-sensitive solid tumors [2-5]. To the best of our knowledge, there were only two cases describing TLS following chemotherapy for metastatic urothelial carcinoma [6,7].

Case Presentation

A 67-year-old female initially underwent a laparoscopic nephrectomy with bladder cuff excision in March of 2015. The surgical pathology showed low grade papillary urothelial carcinoma, with invasion through pelvic wall into peripelvic fibroadipose tissue (AJCC staging pT3). A routine follow-up computed tomography (CT) in August of 2016 was positive for two liver masses in segment 2 and 8 for which she underwent liver lesion biopsy at an outside hospital which was reported benign. Prior to her visit to our cancer center, she has been seeing a naturopathic physician for follow-up of her cancer. A subsequent Magnetic resonance imaging (MRI) three months later showed growth of both liver lesions. In Feb 2017, a CT chest, abdomen and pelvis with contrast at the time of consultation at our cancer center showed Interval development of multiple hepatic masses. The largest is partially necrotic and measures 9.8 × 13.7 cm **(Figure 1)**.

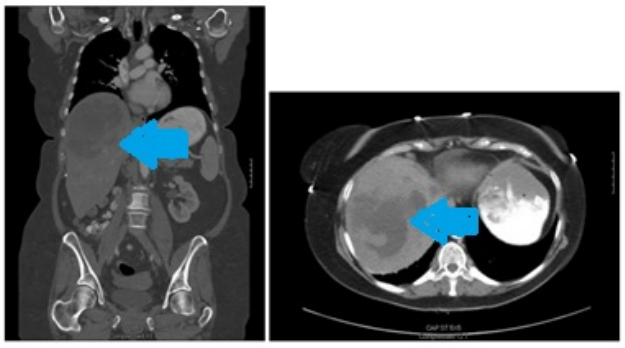

Figure 1 CT chest, abdomen and pelvis with contrast at the time of consultation at our cancer center showed Interval development of multiple hepatic masses. The largest is partially necrotic and measures 9.8 × 13.7 cm (arrow).

She subsequently underwent liver lesion biopsy. The tumor demonstrates strong GATA3, CK7 and CK 20 positivity. Based on the immunophenotypic profile, coupled with the

histomorphology, the findings are consistent with metastatic urothelial carcinoma **(Figure 2)**.

She subsequently received Cycle 1 Day 1 chemotherapy at dose of cisplatin 70 mg/m^2/ gemcitabine 800 mg/m^2. On day 8 visit, the patient was found to have hyperuricemia with uric acid 12 mg/dL (range: 3-6 mg/dL), hypocalcemia with corrected calcium 7.7 mg/dL (range: 8.5-10.3 mg/dL), acute kidney injury with serum creatinine 4.04 mg/dL (range: 0.57-1.11 mg/dL, patient's baseline is 0.85 mg/dL), phosphorus 4.2 mg/dL (range: 2.4-4.7 mg/dL), and lactate dehydrogenase 1,382 units/L (range: 125-243 units/L) **(Table 1)**.

Patient was treated with normal saline hydration and received one dose of rasburicase 7.5 mg intravenous infusion. Most of her laboratory abnormalities improved shortly after treatment initiation and there was no need for inpatient admission. Currently she is responding to ongoing systemic chemotherapy with preservation of quality of life.

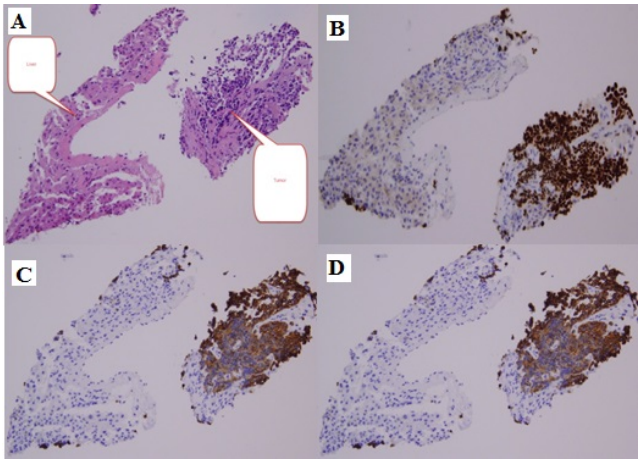

Figure 2 Immunophenotypic profile of liver lesion. Hematoxylin and eosin stain (A), The tumor demonstrates strong GATA3 (B), CK7 (C) and CK 20 (D) positivity. The immunophenotypic profile, coupled with the histomorphology, the findings are consistent with metastatic urothelial carcinoma.

Table 1 Pertinent laboratory findings in 67-year-old female with suspected tumor lysis syndrome.

Laboratory Value (Normal Range)	Pre-chemotherapy	7 days post - Cycle 1 Day 1 chemotherapy	24 hours post-rasburicase 7.5 mg	6 weeks post - Cycle 1 Day 1 chemotherapy
Potassium (3.6-5.3 mmol/L)	4.1	4.0	4.9	4.4
Phosphorus (2.4-4.7 mg/dL)	N/A	4.2	4.6	4.2
Blood Urea Nitrogen (8-25 mg/dL)	9	65	53	25
Serum Creatinine (0.57-1.11 mg/dL)	0.86	4.04	2.99	0.75
Corrected Calcium (8.5-10.3 mg/dL)	9.3	7.7	8.5	8.8
Uric Acid (3-6 mg/dL)	4	12	< 1	2
T. Bili (0.2-1.2 mg/dL)	1.8	0.8	0.6	0.5
Lactate dehydrogenase (125-243 units/L)	1,096	1,382	896	395

Discussion

We searched PubMed/Medline, for articles focused on TLS in patients with urothelial carcinoma published from March 1950 to March 2017. There were two only reported cases of advanced urothelial carcinoma who developed TLS documented in the literature, although only one occurred after gemcitabine [6], another case occurred after PD-1 Immunotherapy [7]. Our case is the third case of reported TLS in patients with urothelial carcinoma **(Table 2)**. All three cases are urothelial carcinoma of renal pelvic origin/upper urinary tract. Tumors of the renal pelvis account for approximately 10% of all renal tumors and only 5% of all urothelial tumors of the urinary tract [8]. A randomized Phase III study comparing cisplatin and gemcitabine (GC) and methotrexate, vinblastine, adriamycin and cisplatin (MVAC) has demonstrated similar efficacy with respect to response, time-to-progression and overall survival, whereas GC is associated with less toxicity than MVAC [9]. Thus, GC is now considered a standard of care for patients with locally advanced and metastatic urothelial cancer.

Both two previous cases were associated with poor clinical outcome leading to the death. Currently, our patient is alive and responding to ongoing systemic chemotherapy with preservation of quality of life. The early identification of TLS and prompt use of rasburicase likely contributed to the better outcome in current case. Rasburicase, a recombinant urate oxidase, may represent an effective alternative to allopurinol in rapidly reducing uric acid levels, improving patients' electrolyte status, and reversing renal insufficiency [4]. The drug initially was studied in pediatric patients with acute lymphoblastic leukemia and aggressive non-Hodgkin

lymphoma; data are lacking in term of the benefit in patients with solid tumors.

Table 2 Review of case reports identifying tumor lysis syndrome in patient with solid tumors.

Author (year) Ref	Primary cancer	Chemotherapy	Liver metastases	Rasburicase	Outcome
Lin (2007)	renal pelvic urothelial carcinoma	gemcitabine	Yes	No	Death
Brunnhoelzl (2017)	renal pelvic urothelial carcinoma	Atezolizumab	Yes	No	Death
This case (2017)	renal pelvic urothelial carcinoma	Cisplatin and Gemcitabine	Yes	Yes	Alive

Rasburicase is currently approved at a dosage of 0.15-0.2 mg/kg once/day for 5 days in pediatric patients with cancer to lower plasma uric acid concentrations and manage TLS [4]. Information on rasburicase dosing in adults is limited, with some data on using rasburicase as a single dose instead of multiple daily doses [10]. Our experience and others confirm that single dose of rasburicase is safe and highly effective in the treatment of chemotherapy-induced hyperuricemia in this setting.

Several of risk factors for TLS have been reported including dehydration, impaired pre-therapy kidney function, hyperuricemia, increased tumor cell proliferation rate and size, and chemosensitivity of the malignancy [1-4]. Our patient was not given prophylaxis before therapy, because the urothelial carcinoma was not considered a risk and no previous published report TLS secondary to current therapy. We speculate the possible contributing factors of developing TLS in this patient include high metastatic tumor volume which was sensitive to GC, which resulted in rapid tumor necrosis. Recent published findings showed patients with somatic alterations in DNA damage response and repair (DDR) genes are associated with improved sensitivity to platinum-based chemotherapy [11,12]. Further research on predictive biomarkers for TLS is warranted.

Conclusion

TLS is an oncologic emergency in the setting of high tumor cell proliferation, tumor burden, and chemosensitivity. Prompt recognition of TLS is essential in decreasing morbidity and mortality associated with it. In future, the integration of biomarkers in chemotherapy offers clinicians the ability to individualize treatment in order to better predict and manage drug toxicities such as TLS, improve quality of life, and maximize the efficacy of therapy.

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