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Tumor Lysis Syndrome Associated with Prostate Cancer: An Under-recognized Oncologic Emergency

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Abstract

Background: Prostate cancer is the second cause of cancer related deaths in men, despite a decrease in incidence and mortality rates in the United States. Tumor lysis syndrome (TLS) is an oncologic emergency with few treatment options. While TLS has been extensively documented in patients with hematological malignancies, it is rarely described in patients with prostate cancer.

The objective of this study was to investigate the clinical characteristics and outcomes of TLS, a rare but life-threatening complication in prostate cancer.

Methods: Retrospective review and pooled analysis.

Results: Fourteen cases of TLS were identified (12 case in published literature and 2 cases from our tumor registry). The median age of patients was 69 years (53-80). The median PSA was 697 (range 66.7-10867). Six cases (43%) of TLS was associated with a variety of treatment regimens, and eight (57%) patients had spontaneous TLS. All patients had extensive bone metastases at the time of presentation, with visceral metastases documented in 50% of TLS cases. The majority of cases were prostate adenocarcinoma (except one case of prostate rhabdomyosarcoma, one case with small cell prostate carcinoma). All of the patients had elevated LDH with other biochemical variables such as uric acid, creatinine, potassium, and phosphorus. The mortality rate was 100% among six cases of treatment related TLS, with a median time to TLS from treatment 6 days (range 1-21), median survival from diagnosis of TLS to death was 8 days (range 2-11). The mortality rate was 37.5% in the eight patients with spontaneous TLS. Each of these cases was treated with aggressive supportive measures, and only one of the patients received rasburicase, while one received allopurinol.

Conclusions: TLS in prostate cancer is associated with very high mortality. TLS should be considered on the differential, when evaluating renal failure and electrolyte derangement in patients with metastatic prostate cancer especially in cases of extensive skeletal involvement and visceral metastases.

Keywords: Prostate Cancer; Spontaneous Tumor Lysis Syndrome (TLS); Oncologic Emergency;

Introduction

Tumor lysis syndrome (TLS) is considered to be an oncological emergency that result in severe metabolic abnormalities, including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, in patients with rapidly proliferating and chemosensitive malignancies, such as acute lymphoblastic leukemia or high-grade lymphoma[1-3]. Although TLS is a well-recognized clinical problem in hematological malignancies, it is understudied in solid tumors and not previously associated with prostate cancer until recently [2-17]. Between 2017 and 2018, our group treated two cases of TLS associated with prostate cancer. We consider these clinical observations deserved further investigation. The objective of this study was to examine the available published information on clinical characteristics, management and outcomes of TLS in patients with prostate cancer.

Patients and Methods

Literature search strategy

Systematic review of the literature was performed by first searching PubMed for "tumor lysis syndrome" and "prostate cancer". The identified case reports and abstracts were reviewed and additional articles of interest were identified from reference lists.

Data collection and statistical analysis

Information regarding the patient (patient age at diagnosis, presentation, and co-morbidities), the tumor (symptoms, histology, Gleason score and AJCC stage), examination results (prostate specific antigen, radiologic investigations), treatment modalities (prostatectomy, chemotherapy and radiation), and the outcome response (response, adverse events, vital status) were recorded, when available. Descriptive statistics, such as frequency counts, medians, and ranges, were used to characterize the pooled sample.

Results

Twelve publications (10 case reports and two meeting abstracts) with total 12 cases of TLS (six cases of treatment related and six case spontaneous TLS) were identified. In addition, we identified two cases of spontaneous TLS identified in our institutional database. The final cohort consistent of a total 14 prostate cancer patients with TLS.

The demographic feature, clinicopathologic features, symptoms and survival outcomes of 14 cases of TLS in prostate cancer were summarized in Table 1.

Table 1: Review of published reports on tumor lysis syndrome in patients with prostate cancer.

Author	Year of diagnosis	Age	Histology/Gleason score/ PSA	Disease burden	Treatment preceding TLS	Time to TLS (days)	Hemodialysis	Rasburicase	Outcome
Sorsche	2004	80	Adenocarcinoma/3+3/348	Bone	Docetaxel, dexamethasone	1			Died
Tanvetyanon	2004	77	Adenocarcinoma/-/10867	Bone, liver	Flutamide and goserelin acetate	6			Died
Wright	2005	60	Adenocarcinoma/3+4/5520	Bone	Paclitaxel	1	Yes		Died
Lin	2007	72	Adenocarcinoma/-/66.7	Bone, liver	Flutamide, leuprolide, dexamethasone, medroxyprogesterone	21			Died
Kaplan	2012	60	Adenocarcinoma/5+4/300	Bone	Radiation therapy to shoulder	6	Yes	Yes	Died
Mazzoni	2016	62	Adenocarcinoma/-/-	Bone, nodes	Radiation, TURBT, bicalutamide		Yes	Yes	Died
Serling-Boyd	2017	56	Adenocarcinoma/5+4/648	Nodes, liver	spontaneous TLS			Yes	Died
Hashem	2010	73	Adenocarcinoma/-/-	Bone	spontaneous TLS		Yes		Died
Zulqarnain	2012	56	Small cell carcinoma/-/-	Bone, liver, nodes	spontaneous TLS			Yes	Alive
Nguyen	2014	72	Adenocarcinoma/-/-	Bone, nodes	spontaneous TLS			Yes	Alive
Ignaszewski	2017	69	Adenocarcinoma/-/-	Bone, liver	spontaneous TLS			Yes	Died
Watanabe	2014	16	Prostate rhabdomyosarcoma/-/-	Bone, nodes	spontaneous TLS			Yes	Alive
Case 1	2016	72	Adenocarcinoma/4+5/746	Bone, nodes	spontaneous TLS				Alive
Case 2	2018	53	Adenocarcinoma/4+4/374	Bone, nodes, lungs	spontaneous TLS		Yes		Alive

The median age of patients was 69 years (53-80). The median PSA was 697 (range 66.7-10867). The majority of cases were prostate adenocarcinoma (except one with prostate rhabdomyosarcoma, one case with small cell prostate carcinoma).

Six cases (43%) of TLS were associated with a variety of treatment regimens, including chemotherapy (14.3%), hormonal (14.3%), radiation therapy (14.3%). Eight (57%) patients had spontaneous TLS.

All patients (100%) had extensive bone metastases with visceral metastases documented in 50% of TLS cases. The median time to TLS from treatment 6 days (range 1-21).

All of the patients had elevated LDH with other biochemical variables such as uric acid, creatinine, potassium, and phosphorus. Each of these cases was treated with aggressive supportive measures, with five patients (35.7%) received hemodialysis.

Regarding TLS prophylaxis, only one of the patients received rasburicase, while three patients received allopurinol.

The mortality rate was 100% among six cases of treatment related TLS, with a median survival from diagnosis of TLS to death was 8 days (range 2-11). The mortality rate was 37.5% in the eight patients with spontaneous TLS.

Discussion

The truce incidence of TLS in prostate cancer is difficult to assess. Based on our clinical observation of two cases of TLS identified in patients treated in 300 bed hospital during last 12 months, we postulated TLS in prostate cancer may be under diagnosed and under-reported. It is now well recognized that the adverse effects (AEs) are underreported in peer-reviewed journal articles documenting the results of clinical trials [18]. In routine clinical setting, TLS can easily miss-classified as acute kidney

injury or electrolytes abnormally. The deficiency of clinical trial design in adequately evaluating and reporting adverse events, in conjunction with lacking of reporting mechanisms in real world, may prevents clinicians and patients from gaining a full understanding of the truce epidemiology and natural history of TLS.

Though well-documented in hematological malignancies, as well as in germ cell tumor and small cell carcinomas, TLS was considered relatively rare in other solid tumors in the era when effective treatment was no available. The advanced age, dehydration, impaired kidney function, are recognized host related risk factors, while large, rapidly growing, and chemosensitive malignancies, are tumor related risk factors. However, our recent study show TLS occur in essentially every tumor type, tumor burden likely more important factor than tissue origin or location [1, 2]. The findings from this study are noteworthy. First, TLS is most often occur in patients with high Gleason score and advanced stage with large disease burden. Bone and visceral metastases documented in 100%, and 50% of TLS cases. Second, TLS in prostate cancer, particularly the treatment related TLS carries a worse prognosis when compared to hematologic malignancies. The lacks of awareness of risk of TLS in prostate cancer, delay in diagnosis and suboptimal management likely contribute to the higher mortality in this population. Education efforts should be made to increase the awareness for this rare but potentially life-threatening oncologic emergency.

Due to the inherent nature of retrospective studies, we were not able to fully assess performance status, co- morbid conditions and clinical manifestations of TLS. Despite the limitations, the present study provides the most updated real world insight regarding the diagnosis and outcomes of TLS patients with prostate cancer. Studies like this report will contribute to the evolving understanding of TLS in prostate cancer and have implications for future treatment paradigms.

Conclusions

In summary, our review highlights the life-threatening nature of TLS, a previously under-recognized complication of prostate cancer. Clinicians should consider TLS as a differential diagnosis when evaluating acute renal failure and electrolyte derangement in patients with metastatic prostate cancer, especially in cases of extensive skeletal involvement. The findings of this study hopefully can improve our current understanding the natural history of TLS and develop optimal multidisciplinary management strategies for this rare, but potential fatal oncologic emergency.

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