Mini Review

Tumor lysis syndrome associated with renal cell carcinoma

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Abstract

Background: Tumor lysis syndrome (TLS) is an oncologic emergency which has been extensively documented in patients with hematological malignancies, but rarely described in patients with renal cell carcinoma (RCC). The objective of this study was to investigate the clinical characteristics and outcomes of TLS, a rare but life-threatening complication in RCC.

Methods: Retrospective literature review and pooled analysis.

Results: Ten cases of TLS were identified in patients with metastatic RCC (eight cases in published literature and two cases from our tumor registry). The median age of patients was 60 years (45-88). Seven cases (70%) of TLS were associated with a variety of treatment regimens, include sunitinib (42%), pazopanib (14.2%), nivolumab (14.2%), nivolumab and ipilimumab (14.2%), and temsirolimus (14.2%). The median time to TLS from treatment was 16 days (14-28). Three (33%) patients had spontaneous TLS. All patients had extensive metastatic disease at the time of presentation, with visceral metastases documented in 100% of TLS cases. The majority of cases were clear renal carcinoma (one case of sarcomatoid, and another with extensive rhabdoid feature). All cases were treated with aggressive supportive measures, and four patients received rasburicase. The mortality rate was 57% among seven cases of treatment related TLS. The mortality rate was 100% in the three patients with spontaneous TLS.

Conclusions: TLS in RCC can occur both after treatment and spontaneously, and is associated with very high mortality. Our findings underscore the importance of heightened awareness, risk assessment, and early prevention of this previously underdiagnosed oncologic emergency.

Keywords: mortality, oncologic emergency, renal cell carcinoma, tumor lysis syndrome

Introduction

Tumor lysis syndrome (TLS) is the most common oncological emergency that results in severe metabolic abnormalities, including hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia in patients with rapidly proliferating and chemosensitive malignancies such as acute lymphoblastic leukemia or high-grade lymphoma [1,2]. Although TLS is a well-recognized clinical problem in
hematologic malignancies, it is understudied in solid tumors and until recently, not previously associated with renal cell carcinoma (RCC) [2-17]. Between 2017 and 2018, our group treated three cases of TLS associated with metastatic RCC. 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 RCC.

Methods

Literature search strategy

Systematic review of the literature was performed by first searching PubMed for “tumor lysis syndrome” and “renal cell carcinoma”. 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 (age at diagnosis, presentation, and comorbidities), tumor (symptoms, histology, grade, and American Joint Committee on Cancer (AJCC) stage), radiologic investigations, treatment modalities (nephrectomy, systemic therapy, and radiation), and 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

Eight case reports comprising a total of 8 cases of RCC-associated TLS (five cases of treatment-related and three cases of spontaneous TLS) were identified. In addition, we identified two cases of treatment-related TLS in our institutional database. The demographic features, clinicopathologic features, symptoms, and survival outcomes of 10 cases of TLS in RCC were summarized in Table 1.

Table 1. Review of published reports on tumor lysis syndrome in patients with RCC

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Gender</th>
<th>Treatment</th>
<th>Histology/Grade</th>
<th>Metastasis</th>
<th>Rasburicase</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholaou</td>
<td>67/F</td>
<td>Sunitinib</td>
<td>Fuhrman grade III</td>
<td>Liver</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>Michels</td>
<td>58/M</td>
<td>Sunitinib</td>
<td>Sarcomatoid features</td>
<td>Liver</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>62/M</td>
<td>Sunitinib</td>
<td>Fuhrman grade III</td>
<td>Liver</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>Norberg</td>
<td>56/M</td>
<td>Spontaneous</td>
<td>Poorly differentiated</td>
<td>Liver</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>Gbaguidi</td>
<td>88/F</td>
<td>Spontaneous</td>
<td>Clear cell RCC</td>
<td>Liver</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>van Kalleveen</td>
<td>58/M</td>
<td>Pazopanib</td>
<td>MSKCC poor risk</td>
<td>Lung, Lymph nodes</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>Sater HA</td>
<td>74/M</td>
<td>Nivolumab</td>
<td>RCC</td>
<td>Lung</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>Allen and Wang</td>
<td>55/M</td>
<td>Spontaneous</td>
<td>RCC with rhabdoid</td>
<td>Liver</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>Wang</td>
<td>66/M</td>
<td>Temsirolimus</td>
<td>Fuhrman grade III</td>
<td>Liver</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>Wang</td>
<td>45/F</td>
<td>Nivolumab and Ipilimumab</td>
<td>Papillary RCC, with prominent tubulopapillary features/IV</td>
<td>Liver/Lung</td>
<td>Yes</td>
<td>Survival</td>
</tr>
</tbody>
</table>

RCC: Renal cell carcinoma, MSKCC: Memorial Sloan Kettering Cancer Center

Patients had a median age of 60 years (45-88) and were predominantly male (70%). The majority (80%) of cases were clear cell carcinoma (one with sarcomatoid and another with extensive rhabdoid features); one patient (10%) had chromophobe histology and another (10%) had papillary RCC, with prominent tubulopapillary. In all cases, patients presented with bulky metastases, high grade disease, and hepatic...
metastases. All of the patients had elevated LDH with other biochemical variables such as uric acid, creatinine, potassium, and phosphorus. Seven cases (70%) of TLS were associated with a variety of treatment regimens including sunitinib (42%), pazopanib (14.2%), nivolumab (14.2%), nivolumab and ipilimumab (14.2%), and temsirolimus (14.2%). The median time to TLS from initiation was 16 days (14-28). Three (33%) patients had spontaneous TLS (STLS) without any active cancer treatment. All patients had extensive metastatic disease at the time of presentation, with visceral metastases documented in 100% of TLS cases. All cases were treated with aggressive supportive measures including intravenous hydration, and four patients received rasburicase. The mortality rate was 57% among seven cases of treatment-related TLS. The mortality rate was 100% in the three patients with spontaneous TLS.

Discussion

Though well-documented in hematological malignancies, TLS was considered relatively rare in solid tumors in the era when the effective treatment was not available. However, our recent study shows significant increase in cases of TLS associated with solid tumors [4]. TLS occurs in essentially every tumor type, such that the tumor burden itself is likely the more important factor than the tissue origin or location [3-7]. High tumor burden has classically been defined via three concrete measurements: bulky disease (>10 cm), elevated LDH (>2x upper limit of normal), and elevated WBC (>25,000) [9]. Additionally, large tumor burden is characterized by advanced stage via presence of distant organ metastasis (e.g., liver) [8,15]. Interestingly, 100% of the TLS cases reviewed in this study ultimately presented with distant organ metastases and a majority showed LDH elevations greater than two times the upper limit of normal either at baseline or at the time of TLS diagnosis. The rate of STLS (50%) seems higher in metastatic RCC patients than patients with solid tumor (24%).

RCC is the most common solid lesion of the kidney, and more than 40% of patients eventually die from this disease. Although the true incidence of TLS in RCC is difficult to assess, we postulate that TLS in RCC may be underdiagnosed and underreported [3-7]. Several studies showed that a substantial proportion of TLS cases presenting to the emergency department (ED) were not recognized as such. In a routine clinical setting, TLS can easily be misclassified as acute kidney injury or an electrolytes abnormality. It is now well-recognized that the adverse effects are underreported in peer-reviewed journal articles documenting the results of clinical trials [18]. The deficiency of clinical trial design in adequately evaluating and reporting adverse events, in conjunction with the lack of efficient reporting mechanisms in the real world, may prevent clinicians and patients from gaining a full understanding of the true epidemiology of TLS.

This study presents several noteworthy findings. First, TLS generally occurs in patients with advanced stage cancer with large disease burdens. Visceral metastases were documented in all 10 TLS cases in this study (Table 1). Second, TLS in RCC, and particularly spontaneous TLS, carries a worse prognosis when compared to hematologic malignancies. Lack of awareness about the risk of TLS in RCC, delayed diagnosis, and suboptimal management likely contribute to the higher mortality in this population. Education efforts are urgently needed to increase the awareness for this rare but potentially life-threatening oncologic emergency [3-4]. The most important finding from our study is that TLS associated with RCC occurs later than previously expected: the median time from treatment to TLS was 16 days with a range of 14 to 28 days. This finding is particularly important because it is outside the usual timeframe that is observed with conventional chemotherapy in routine clinical setting [4-7]. The current guidelines and consensus on diagnosis and management of TLS were based on pediatric hematologic tumors and established more than one decade ago [8-9]. Furthermore, this was at a time when effective therapies for solid tumors such as RCC were not available, supporting the need to revise current guidelines. A call to revisit and refine the risk stratification of TLS in the new targeted therapy and immunotherapy era is necessary based on current findings. For high-risk patients with predisposing factors, we suggest that it is critical to monitor patients’ electrolytes and renal function at least weekly during the first cycle of therapy.

Due to the inherent nature of retrospective studies, we were not able to fully assess several factors such as performance status and comorbid conditions that may impact the outcome of TLS. Despite the limitations, the present study provides the most updated real-world insight regarding the diagnosis and outcomes of TLS in patients with RCC. Our study will contribute to the evolving understanding of TLS in solid tumors and have implications for future cancer treatment paradigms in this targeted therapy and immunotherapy era.

Conclusions

Our review highlights the life-threatening nature of TLS, a previously under-recognized oncologic emergency of RCC, especially in elderly patients with extensive liver metastases. It is also crucial for clinicians to recognize that TLS associated with RCC treatment may occur later than expected. A call to revisit and refine the risk stratification of TLS in the new targeted therapy and immunotherapy era is necessary based on current findings.
Conflict of interest
All authors declare that they have no conflict of interest.

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References