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The Clinical Features, Outcome and Prognosis of Spontaneous Tumor Lysis Syndrome in Solid Tumor

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Abstract

Purpose: The main objective of this study was to determine the clinical features, outcome and prognosis of spontaneous tumor lysis syndrome (s-TLS) in solid tumor.

Materials and Methods: Retrospective pooled analysis of clinical characteristics and outcomes of published cases of TLS in solid tumor from 1960 to 2017.

Results: Among 132 cases of TLS in solid tumor identified in published literature, 100 (76%) occurredafter active cancer therapy; 32 cases occurred spontaneously. The median age of patients with s-TLS was 58.5 years (15-88). Male to female ratio was 3:1. Gastrointestinal and genitourinary cancer contribute to the majority (56%) of all sTLS cases. s-TLS tend to have high rate of acute kidney injury (AKI) and elevated Lactate dehydrogenase (LDH) than treatment related TLS (t-TLS). The in hospital mortality rate of s-TLS and t-TLS were 56.3% and 54%, respectively.

Conclusion: Similar to treatment induced TLS, the development of s-TLS in solid tumor is associated with very high mortality. Spontaneous TLS should be considered in the differential diagnosis for patients who demonstrate electrolyte abnormalities or renal failure in the setting of newly diagnosed malignancy even without cytotoxic treatment.

Keywords: Oncologic emergency; Tumor Lysis Syndrome (TLS); Spontaneous Tumor Lysis Syndrome (s-TLS); TLS secondary to treatment (t-TLS); Solid tumor; Overall survival (OS); Prognosis

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Introduction

Tumor lysis syndrome (TLS) is the most common oncologic emergency, and although historically seen in the context of initial chemotherapeutic treatment of hematologic malignancies, recently, increasing attention being paid to the rising incidence of spontaneous tumor lysis syndrome (s-TLS) and TLS secondary to treatment (t-TLS) of solid tumors [1,2]. Data regarding clinical features, treatment, and survival outcomes of s-TLS in solid tumors are limited to case reports [3-33]. There is no published large study examine s-TLS in solid malignancies.

The main objective of this pooled analysis was to describe the clinical features, treatment, prognosis, and outcome of patients with s-TLS in solid malignancies. In additon, we seek to determine if there is a difference in clinical outcome of s-TLS and t-TLS.

Materials and Methods

Literature search strategy

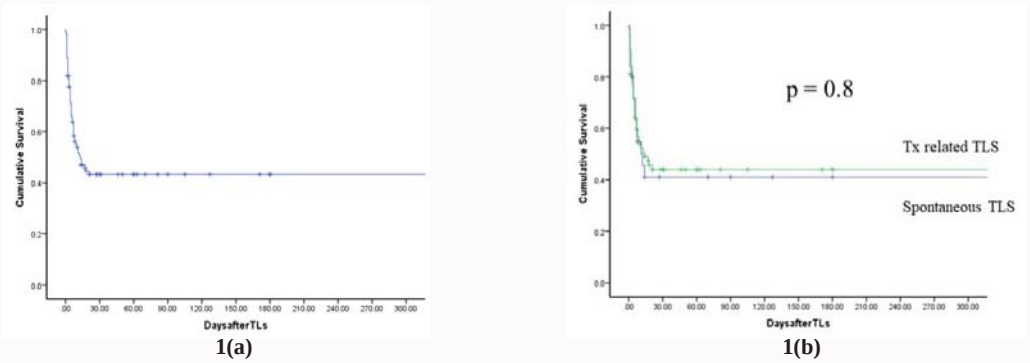
A systematic review of the literature was performed by first searching PubMed for "tumor lysis syndrome" and "solid tumor". Case reports were reviewed and additional articles of interest were identified from reference lists.

Data collection

Demographic information (including age, time of diagnosis of TLS); clinical data (including clinicopathologic features), laboratory, radiographic findings, treatment and outcomes were collected.

Statistical analysis

Patients were divided into s-TLS and t-TLS. Baseline demographics, tumor characteristics including medians, ranges and frequencies were compared using descriptive statistics. A chi-squared test was used as appropriate for comparison of categorical variables.



1(a) 1(b)

Figure 1: (a) Kaplan Meier survival curve of entire cohort of 132 patients with solid tumors and tumor lysis syndrome. (b) Survival distribution stratified by etiology.

Survival was calculated according to the Kaplan-Meier method and the survival curves were compared by univariate analysis with the long-rank test. Overall survival (OS) was defined as the time from the date of TLS diagnosis to the date of death. Statistical significance was defined as a p-value <0.05. All analyses were performed using SPSS ver. 24.0 (SPSS Inc., Chicago, IL).

Results

Patient and tumor characteristics

A total of 132 patients with TLS in solid tumor were included in this study. The majority of patients 100 (76%) of TLS was associated with a variety of treatment regimens, including chemotherapy, target agents, immunotherapy, hormonal therapy, radiation therapy, chemoembolization, and surgery. The rest 32 (24%) patients had s-TLS before any cancer treatment.

The median age of 32 patients who developed s-TLS was 58.5 years (15-88). Male to female ratio was 3:1. The most common sites were gastrointestinal (29%) and genitourinary (17%). Liver metastasis was identified in 81% of patients.

Comparison of spontaneous and treatment related TLS

A comparison was made between patients with s-TLS and t- TLS. The demographic feature, clinicopathologic features, symptoms and survival outcomes of the two groups were summarized in Table 1. Gastrointestinal and genitourinary cancer contributes to the majority (56%) of all sTLS cases. In addition, s-TLS tend to have higher rate of AKI and elevated LDH than t-TLS. The differencein the frequency of hyperphosphatemia in s-TLS (68%) and TTLS (80%) was noted, however, not statistically significant in our analysis.

Outcomes and prognostic factors

The median overall survival (OS) of entire cohort was 13 months with 95% Confidence Interval (4.3-21.7). During study period, the mortality rate for s-TLS and t-TLS were 56% and 54%, respectively (p=0.97).

Figure 1a showed Kaplan Meier survival curve of entire cohort of 132 patients with solid tumors and tumor lysis syndrome. Figure 1b showed survival distribution stratified by etiology. Patients withspontaneous TLS had a very poor overall survival, similar to those treatment related TLS patients.

Discussion

Although previously thought quite rare, increasing numbers of case reports documenting TLS in solid malignancies have been published over the last decade [3-33]. This may be due to increased awareness and surveillance, as well as improved efficacy of cancer treatment. The underling mechanisms and triggers for spontaneous TLS have not been well described. It was speculated that necrosis of bulky tumor masses as a result of rapid growth, insufficient blood supply and subsequent hypoxia, could initiate the pathological cascade of TLS and activate inflammatory mechanisms that ultimately resulting in systemic cytokine storm, ARF and fetal arrhythmias [1,2]. Although advanced age, dehydration, impaired kidney function, were recognized host related risk factors, while large, rapidly growing and chemosensitive malignancies such as germ cell tumor and small cell lung cancer, were recognized as tumor related risk factors, however, our study show TLS occur in essentially every tumor type, tumor burden likely more important risk factor than tissue origin or location. In this largest study TLS in solid tumors; 32 cases of 132 TLS cases (24%) were s-TLS. Consistent with findings in other study, TLS is most often occur in patients with high tumor grade and/or advanced stage. Liver metastases documented in 81% of all s-TLS cases in our cohort.

Table 1: Comparison of the demographic and clinical characteristics of spontaneous tumor lysis syndrome (s-TLS) and TLS secondary to treatment (t-TLS) of solid tumors.

N (%)	All	Spontaneous TLS	Treatment related TLS	P value
Age, years ≥ 60	58 (43.9%)	15 (46.9%)	43 (43%)	0.7
Sex, male	83 (62.9%)	24 (75%)	59 (59%)	0.1
Breast cancer	11 (8.3%)	1 (3.1%)	10 (10%)	0.22
Liver metastasis	97 (73.5%)	26 (81.2%)	71 (71%)	0.25
Hyperphophatemia	102 (77.3%)	22 (68.8%)	80 (80%)	0.4
Hyperuricemia	114 (83.4%)	27 (84.3%)	87 (87%)	0.93
Acute kidney injury	116 (87.9%)	28 (87.5%)	86 (86%)	0.01
Elevated LDH	94 (71.2%)	24 (75%)	70 (70%)	0.03
Death	72(54.5%)	18 (56.3%)	54 (54%)	0.95

Table 2: Patients with solid tumors and tumor lysis syndrome per tumor location.

	Spontaneous TLS	Treatment related TLS	Total
GI	10	28	38
GU	8	16	24
Breast	1	10	11
Lung	5	15	20
Skin	1	13	14
Others	7	18	25

Our analysis show s-TLS have high rate of acute kidney injury (AKI) and elevated lactate dehydrogenase (LDH), than t-TLS. As seen in this study, hyperphosphatemia was previous thought less frequently in s-TLS than that in t-TLS. Although the difference of frequency of hyperphosphatemia in s-TLS (68%) and t-TLS (80%) was not statistically significant in our analysis (Table 2), likely due to the small sample size. The potential explanation for this observation is that highly proliferative tumor recycle the phosphorus rapidly for the synthesis of new cells in tumors [3,27]. A large, prospective, multi-institutional TLS registry likely the provide a more definitive answer to this question.

Two important findings from this study are noteworthy: first, TLS in solid tumors carries a worse prognosis when compared to hematologic malignancies. The reported mortality of patients with hematologic malignancies and TLS, 6-month mortality was 21%. The lacks of awareness of risk of s-TLS in solid tumor likely contribute to the higher mortality in this population. Urgent education efforts should be made to increase the awareness for this rare but potentially life-threatening oncologic emergency. Second, the prognosis of both s-TLS and t-TLS in solid tumor are similarly poor. In this study cohort, the mortality rate for s-TLS and t-TLS in solid tumors were 56%, and 54% respectively (p=0.97). The underlying cause of extremely high mortality is s-TLS is unknown. Thefrequent clinical observation of multi-organ failure, unstable circulatory dynamics in the patients who died after TLS suggested the possibility of involvement of humoral mediators [34-36]. We hypothesized that, in addition to electrolyte abnormalities and accumulation of metabolites due to tumor cell lysis, cytokine storm or hypercytokinemia might play a pivotal role in the pathophysiology of TLS. We proposed prospective evaluation of cytokines as biomarker of TLS and role of continuous hemodiafiltration (CHDF) in these patients. This research may lead novel strategy to decrease the high mortality of TLS in solid tumor. At this time, medical prophylaxis of TLS is not the standard of care for patients undergoing treatment of solid tumors. Based on our findings, s-TLS should be considered in the differential diagnosis of patients with elevated LDH and AKI and a significant burden of metastatic disease, particularly in the setting of hyperuricemia, hyperkalemia and hyperphosphatemia.

There are several limitations to this study. First, due to the inherent nature of retrospective studies and lack of accessibility to original medical records, we were unable to fully assess patient's performance status, comorbid conditions and clinical manifestations of TLS or adverse effects from active cancer therapy. Despite the limitations, the present study provides the most comprehensive information regarding the diagnosis and outcomes of TLS patients with solid tumors. The findings of this study would help improve our current understanding and develop optimal multidisciplinary management strategies for this rare, but potential fatal condition.

Conclusion

TLS is a rare life-threatening condition increasely encountered by oncologists, Emergency Department physicians, and critical care teams. Our findings underscore the importance of heightened awareness, risk assessment and early prevention to reduce this serious, potential fetal complication of solid tumors.

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