ORIGINAL ARTICLE

Association of Biochemical Derangements with Tumor Lysis Syndrome in Common Haematological Malignancies

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Abstract

Objective: To evaluate the frequency of Tumor lysis syndrome (TLS) in patients with common hematological malignancies after first course of chemotherapy and to determine the association of different biochemical derangements in making the diagnosis of TLS.

Methods: Cohort study was conducted in INMOL from October 2012 to October 2013. All patients newly diagnosed with hematological malignancies were included. Blood samples were taken for different biochemical tests (uric acid, potassium, phosphorous, calcium, and creatinine). On the day of admission base line samples for these parameters labeled as day zero and further samples were taken for 5 consecutive days after induction chemotherapy labeled as day1,2,3,4,5.Cairo bishop criteria were used, according to which two or more above biochemical derangements should be present for making diagnosis of TLS

Results: Only one patient with AML fulfilled the criteria for TLS and 23 patients with different hematological malignancies at different ages showed different type of biochemical derangements. Statistically significant difference ($p<0.05$) found in uric acid levels between (D0 vs D1,D0 vs D2, D0 vs D3, D0 vs D4 and D0 vs D5) when compared before and after chemotherapy. Regarding other parameters PO4, K, Ca and Cr did not showed any significant difference ($p>0.05$).

Conclusion: There was an association of biochemical derangements with TLS in making the diagnosis by using the Cairo bishop criteria as a diagnostic tool and prompt diagnosis of TLS with the help of these biochemical derangements will help to reduce the mortality and morbidity in malignant patients, after chemotherapy. Prophylactic therapy had a strong impact on patient outcome, decreasing the frequency of TLS.

Key words: *chemotherapy, crequency, cematological malignancies, patients, tumorlysis syndrome*.

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Introduction

Tumor lysis syndrome (TLS) is an oncological emergency, results from massive lysis of malignant cells[(1)], characterized by hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcaemia[(2)]. It is observed in patients with bulky, rapidly proliferating, treatment-sensitive tumors, in particular hematological malignancies such as lymphocytic leukemia and high-grade non-Hodgkin's lymphoma.[(3)] It is less common in AML (acute myeloid leukemia) and could occur with CML (chronic myeloid leukemiain blast crises) with the administration of combined cytotoxic therapy[(4,5)], but rarely observed in patients

with solid tumors.[6]

Tumor lysis syndrome (TLS) develop especially after use of cytotoxic drugs (chemotherapy, corticosteroids, radiation, hormonal agents, and biological response modifiers)[3], shortly after start of effective cytotoxic therapy, usually before or within one week after starting the specific anti-leukemic therapy[7]. It may occur less frequently spontaneously, before any therapy[8]. Being a critical and emergency situation, it requires immediate intervention[9]. TLS depends on patients risk factors such as baseline hyperuricemia, bulky tumor burden (more than 10cm) with first course of chemotherapy, concentrated and acidic urine pH, elevated serum LDH, elevated WBC (more than 100000/µl), hematological malignancies with a high proliferative index, dehydration[10], pre-existing renal damage, tumor infiltration of the kidney, obstructive uropathy and advanced age[11]. Prevalence of TLS has also been categorized as laboratory and clinical TLS (as mentioned in the criteria for classification of TLS). Laboratory TLS observed more frequently than clinical TLS and incidence of laboratory TLS was approximately 12% and clinical TLS was 5%[12]. When cancer cells lyse, they release potassium, phosphate, calcium, and nucleic acid. Nucleic acids are metabolized in to uric acid. TLS occur when more potassium, phosphate, nucleic acid and cytokines are released during cell lysis, the body homeostatic mechanisms[13]. Renal excretion is the primary means of clearing xanthine, urate and phosphate, which can precipitate as calcium phosphate crystals in any part of the kidney and cause inflammation, obstruction and acute renal injury[14,15]. Uric acid can induce acute renal injury by intra-renal crystallization[16,17]. Hyperkalemia can cause serious dysrrhythmias. Hyperphosphatemia can cause secondary hypocalcemia, leading to tetany, seizures and dysrrhy-thmias[18]. Hyperkalemia is often the earliest laboratory manifestation. Hyperkalemia and hyperphosphatemia results directly from rapidly cell lysis. Tumor lysis also releases cytokines that cause a systemic inflammatory response syndrome and often multiorgan failure[19,20].

Methods

Patients with newly diagnosed hematological malignancies were selected from hematology department of Institute of Nuclear Medicine and Oncology, Lahore (INMOL) and tests were performed in department of Biochemistry and Chemical

Table 1: *Cairo Bishop Criteria for Diagnosis of Tumor Lysis Syndrome*[21]

Sr. #	Biochemical derangements	Laboratory TLS	Clinical TLS
1	Hyperuricemia	Uric acid >8.0 mg/dl in adults 0r Above the upper limit of the normal range for age in children	
2	Hyperphosphatemia	Phosphorous >4.5 mg/dl in adults or >6.5 mg/dl in children.	
3	Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dys rrhythmia or sudden death probably or definitely caused by hyperkalemia.
4	Hypocalcemia	Corrected calcium <7.0 mg/dl or ionized calcium <1.12mg/dl	Cardiac dysrrhythmia,sudden death, seizure, neuromuscular irritability (tetany, parasthesias, muscular twitching, corpopedal spasm, Trou -sseau s sign, Chvosteks sign, or broncho-spasm), hypotension, or heart failure probably or definitely caused by hypocalcemia.
5	Acute kidney injury	Not applicable	Increase in the serum creatinine level of 0.3 mg/dl or >1.5 times the upper limit of normal range or the presence of oliguria , defined as an average urine output of <0.5 ml/kg/hr for 6 hrs.
		Laboratory TLS requires two or more of the above metabolic abnormalities occur within 3 days before or up to 7 days after initiation of therapy.	Clinical TLS is present when laboratory TLS is accompanied by an increase creatinine level, seizures, cardiac dysrrhythmia, or death.

pathology, Sheikh Zayed hospital, Lahore. Sample size of 38 patients were estimated by using 90% confidence level and 10% margin of error with expected 16.6% incidence[22] of TLS in cancer patients under treatment. Inclusion criteria of patients were newly diagnosed indoor patients with haematological malignancies of all ages and both gender planned to receive first course of chemotherapy. First sample was taken before start of chemotherapy and then further samples were taken for consecutives 5 days after start of induction therapy. Exclusion criteria were patients other than hematological malignancies, patients with acute and chronic renal failure other than consequence of TLS, any other cause of hyperphosphatemia like (PTH releasing malignant tumors of bones, increase vitamin D intake), any other cause of hyperkalemia like (diabetic ketoacidosis, massive hemolysis), any other cause of hypocalcemia like (hypoalbuminemia, surgically induced hypoparathyroidism). These patients participated willingly with prior consent to undergo tests. History of the subjects, demographic information, and biochemical results were recorded in a Performa shown in Annexure II. Prior to collection of blood sample, skin of donors(patients with haematological malignancies) was thoroughly cleaned with ethanol. For each subject 5 ml of whole venous blood was taken, allowed to clot for 20 -30 minutes and then centrifuged to take clear serum which was preserved in labeled eppendroff tubes at -20oC for analysis of different biochemical parameters i-e serum uric acid, phosphate, calcium, creatinine and potassium levels. The biochemical tests were done using "Siemens Health Care Diagnostics kits" on serum samples for uric acid, phosphate, calcium, creatinine and potassium levels. All these tests were performed on fully automated chemistry analyzer Dimension RXL RMS (Siemens), which were available in department of Biochemistry and Chemical pathology, Sheikh Zayed Hospital, Lahore. Quality control was maintained by using control sera by Humatrol. Both normal (Humatrol N) and pathological (Humatrol P) controls were used. Statistical analysis was conducted on Statistical Package for Social Sciences (SPSS) version (20.0). Results of serum uric acid, potassium, phosphorous, calcium, creatinine were expressed as mean ± SD. One-way repeated measure ANOVA was used to find the difference in uric acid, potassium, phosphorous, calcium, creatinine between different days. Further Post Hoc test- Bonferroni was applied. p value of less than 0.05 considered statistically significant .Simple bar charts were used to compare the levels of uric acid, potassium, phosphorous, calcium and creatininein different days.

Results

The current study was carried out in 38 newly diagnosed hematological malignant patients.10 (26.3%) were in age ranges of 5 – 15 years & 20 (52.6%) were in ranges of 16 – 30 years and 08 (21.1%) were > 30 years of age. This shows that maximum patients were in age ranges of 16 – 30 years. (Tab.1)while 27 (71.1%) were males & 11 (28.9%) were females. This shows male and female ratio was 2.4:1 (Tab.2).Distribution of hematological malignant patients were, out of 38 patients, 26 (68.5%) of Pre B ALL, 04 (10.5%) of Pre T ALL, 07(18.4%) of with AML and 01(2.6%) was Lymphoma patient. This shows that Pre B ALL patients were more as compared to Pre T ALL and difference was highly significant ($p<0.01$) statistically (Fig.3). In this study, out of 38 patients, only 01 (2.6%) patient of AML developed TLS in D1, D2, D3, D4 & D5 after chemotherapy (Fig.4).

Table 2: *Distribution of Subjects by Age Groups*

Age (Years)	No. Of Patients	%
5-15	10	26.3
16-30	20	52.6
>30	08	21.1
Total subjects	38	100

Table 3: *Gender Distribution of Patients*

SEX	No. Of Patients	%
Males	27	71.1
Females	11	28.9
Total subjects	38	100

Regarding isolated biochemical derangements 23(60%) patients showed different type of biochemical derangements (Fig.5) In this study statistically significant difference (p value <0.05) found only in uric acid levels between (D0 vs D1,D0 vs D2, D0 vs D3, D0 vs D4 and D0 vs D5) when compared before and after chemotherapy.(Tab6) Regarding other parameters phosphorous, potassium, calcium and creatinine did not show any significant difference (p value >0.05).(Tab7,8,9,10)

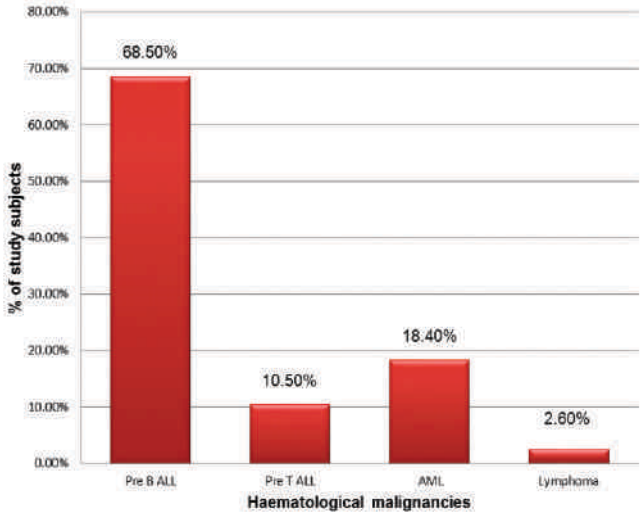

Fig 3: *Bar graph shows percentage of study subjects in different haematological malignancies*

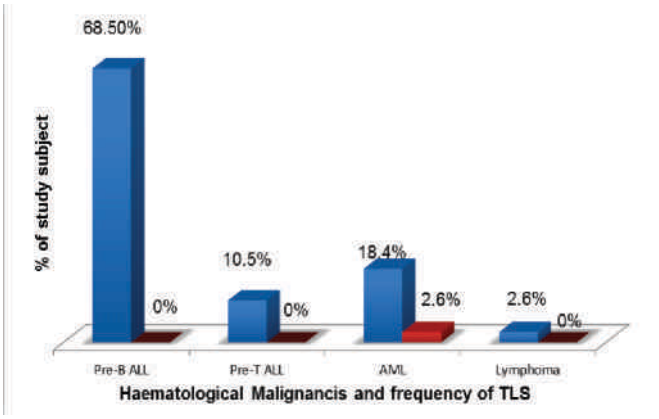

Fig 4: *Bar graph shows frequency of TLS in study subjects of haematological Malignancies after Chemotherapy*

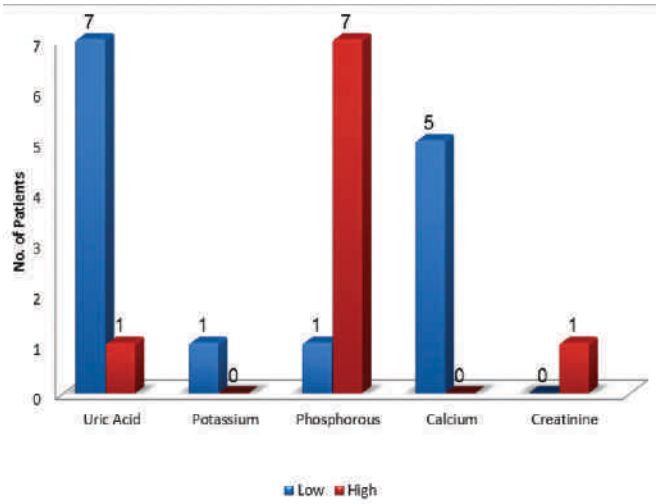

Fig 5: *Bar graph shows Distribution of isolated biochemical derangements(high and low) in 23 patients*

Table 4: *Levels of serum uric acid before and after chemotherapy in all 38 patients*

	Uric Acid (mg/dl)					
	D0	**D1**	**D2**	**D3**	**D4**	**D5**
Mean ± SD Values	4.6±1.36	3.8±1.48	3.8±1.56	3.7±1.66	3.6±1.37	3.7±1.36
Observed Ranges	2.0 --8.0	0.7—6.9	1.4—8.3	1.1—9.2	0.5—6.3	0.9—7.4

One-way repeated measure ANOVA was used to find the difference in uric acid in different days.
Further Post Hoc test- Bonferroni was applied

Statistical Analysis: D0 vs D1 ($p<0.05$) (Significant) D0 vs D2 ($p<0.05$) (Significant)
D0 vs D3($p< 0.05$) (Significant) D0 vs D4 ($p<0.05$) (Significant)
D0 vs D5 ($p<0.05$) (Significant)

Table 5: *Serum potassium level before and after chemotherapy in 38 patients*

	Potassium (mmol/liter)					
	D0	**D1**	**D2**	**D3**	**D4**	**D5**
Mean ± SD mmol/liter	3.7±0.76	3.7±0.69	3.8±0.80	3.6±0.75	3.7±0.74	3.6±0.74
Observed ranges	2.4-5.7	2.4-5.6	2.5-5.6	2.3-5.5	2.5-5.5	2.3-5.0

One-way repeated measure ANOVA was used to find the difference in potassium in different days.
Further Post Hoc test- Bonferroni was applied

Statistical Analysis: D0 vs D1 (p>0.05)(NS) D0 vs D2 (p>0.05)(NS)
D0 vs D3(p> 0.05)(NS) D0 vs D4 (p>0.05)(NS) D0 vs D5 (p>0.05)(NS)

Table 6: *Serum phosphorus level before and after chemotherapy in all 38 patients*

	Phosphorus(mg/dl)					
	D0	**D1**	**D2**	**D3**	**D4**	**D5**
Mean ± SD (mg/dl)	3.4±0.79	3.6±0.98	3.5±0.86	3.7±1.04	3.7±0.97	3.6±1.01
Observed Ranges	2.0-7.0	1.8-6.4	1.5-5.5	2.1-5.9	0.7-5.6	0.7-5.3

One-way repeated measure ANOVA was used to find the difference in phosphorous in different days.
Further Post Hoc test- Bonferroni was applied

Statistical Analysis: D0 vs D1 (p>0.05)(NS) D0 vs D2 (p>0.05)(NS)
D0 vs D3(p> 0.05)(NS) D0 vs D4 (p>0.05)(NS) D0 vs D5 (p>0.05)(NS)

Table 7: *Serum calcium level before and after chemotherapy in all 38 patients*

	Calcium (mg/dl)					
	D0	**D1**	**D2**	**D3**	**D4**	**D5**
Mean ± SD mg/dl	8.0±0.59	8.02±0.63	7.8±0.60	7.8±0.52	7.9±0.58	7.6±1.04
Observed Ranges	7.0-9.5	6.5-10.0	6.4-9.0	6.9-9.1	6.2-9.0	3.4-9.0

One-way repeated measure ANOVA was used to find the difference in calcium in different days.
Further Post Hoc test- Bonferroni was applied

Statistical Analysis: D0 vs D1 (p>0.05)(NS) D0 vs D2 (p>0.05)(NS)
D0 vs D3(p> 0.05)(NS) D0 vs D4 (p>0.05)(NS) D0 vs D5 (p>0.05)(NS)

Table 8: *Serum Creatinine level before and after chemotherapy in all 38 patients*

	Creatinine (mg/dl)					
	D0	**D1**	**D2**	**D3**	**D4**	**D5**
Mean ± SD mg/dl	0.75±0.24	0.73±0.24	0.8±0.44	0.8±0.0.50	0.78±0.26	0.8±0.35
Observed Ranges	0.4-1.4	0.3-1.4	0.3-3.1	0.2-3.4	0.3-1.7	0.4-2.4

One-way repeated measure ANOVA was used to find the difference in creatinine in different days.
Further Post Hoc test- Bonferroni was applied

Statistical Analysis: D0 vs D1 (p>0.05)(NS) D0 vs D2 (p>0.05)(NS)
D0 vs D3(p> 0.05)(NS) D0 vs D4 (p>0.05)(NS) D0 vs D5 (p>0.05)(NS)

Discussion

This study was performed to evaluate the frequency of tumor lysis syndrome in hematological malignancies after induction chemotherapy therapy and to determine the association of these biochemical derangements with TLS in making the diagnosis of TLS, by using Cairo bishop criteria in the same patients. The current study consisted of analysis of serum uric acid, phosphate, potassium, calcium and creatinine levels in all study subjects before and after chemotherapy for consecutive 5 days.

In this study, data showed that despite supportive therapy, biochemical derangements remained a clinical problem and can be fatal in malignant patients who received chemotherapy especially during induction phase. These patients should be monitored closely and on daily basis for these biochemical derangements. These biochemical derangements can act as a diagnostic tool for TLS. This study adopted a criteria laid down by Cairo and Bishop for diagnosis of TLS[21]. Another research conducted in Egypt, followed the same Cairo and Bishop criteria, published in 2012 conducted by Hashem A and coworkers in clinical pathology, pediatric and medicine department in Assuit University, in which 60 diagnosed ALL children aged <18 years were studied regarding clinical and laboratory approach for the identification of risk for tumor lysis syndrome in children with acute lymphoblastic leukemia, TLS was defined by the presence of >2 laboratory abnormalities occurring in time of interest (before and 5 days after initiation of chemotherapy). Out of 60 patients 45% met the criteria for TLS[23].

The variations in patients Cohort and deficiency of standard criteria, contributing a wide range of reported incidence and so far no such study ever been conducted in Pakistan in which serial monitoring of patients is done to evaluate TLS. In one retrospective study carried out by Yasmeen N and Ashraf S in 2009, who assessed the epidemiology, clinical presentation and laboratory features in 611 childhood acute lymphoblastic leukemia patients and reported the frequency of TLS (13%) in these patients.(24)The less frequency of TLS corresponds to our study. In current study out of 38 patients only 1(2.6%) patient of AML developed TLS showing pre-chemotherapy elevated uric acid and creatinine levels on admission and had hyperuricemia, hypocalcaemia, hypokalemia and increase creatinine levels in post chemotherapeutic period in different days. This patient fulfilled the criteria for laboratory as well as clinical TLS.

In current study isolated biochemical derangements were observed in 23(60%) of patients out of total 38 patients in post chemotherapeutic period from D1 to D5. Out of these 23(60%) hypouricemia were found in 7(18.4%), hyper phosphatemiain 7(18.4%), hypocalcemia in 5(13.2%), hypophosphatemia in 1(2.6%) patient, hypokalemia in 1(2.6%) patient hyperuricemia in 1(2.6%) patient and increase creatinine in 1(2.6%) of patients.

Regarding different observed parameters levels when compared between D0 vs D1, D0 vs D2, D0 vs D3,D0 vs D4, D0 vs D5, only statistical significant difference found in uric acid levels(p value <0.05) when compared between D0 vs D1, D0 vs D2, D0 vs D3, D0 vs D4, D0 vs D5 (Tab 6). It was observed that at the time of admission many patient presented with base line hyperuricemia and these patients prophylactically treated with allopurinol and other uricosuric drugsled to hypouricemia in post chemotherapeutic period (D1, D2, D3, D4, D5) while regarding phosphorous, potassium, calcium, creatinine levels when compared between pre and post chemotherapeutic period no significant difference were found (p value >0.05).

In current study another finding was hyperphosphatemia in 7(18.4%) hypocalcaemia in 5(13.2%) among all 38 patients. Hyperphosphatemia was probably because malignant hematologic cells contained upto 4 times more intracellular phosphate compared with normal mature lymphoid cells and acute destruction of tumor cells due to chemotherapy prevented the reuse of phosphate. Precipitation of calcium phosphate occur when solubility products of Ca and PO_4 is exceeded, leading to hypocalcemia. Acute nephrocalcinosis or precipitation of Ca, PO_4 in the renal tubules with an inflammatory response lead to acute renal failure. In this study the unusual finding is occurrence of hyperphosphatemia and hypocalcaemiain different patients, it is strongly associated with adequate hydration given to these patients which prevents the precipitation of Ca and PO_4 in the renal tubules, while isolated hypocalcaemia in these patient is

associated with hypoalbuminemia, use of corticosteroid drugs as a part of chemotherapy, diarrhea, and alkalosis..

In current study absence of hyperuricemia was unusual because it was believed to be the most commonly observed derangement in patient with chemo sensitive tumor. In this study only 1(2.6%) patient showed hyperuricemia despite prophylactic measures leading to renal failure, it was observed in who was treated with allopurinol, prior to chemotherapy. Allopurinol was ineffective at reducing uric acid formed prior to chemotherapy. This Patient had elevated prechemotherapy D0 uric acid 8.4 mg/dl and creatinine level 1.4 mg/dl. Both pretreatment hyperuricemia and increased creatinine level proved to be poor prognostic factors[10,11].

In this study another unusual finding was hypokalemia in contrast to usual hyperkalemia in TLS because in other studies hyperkalemia included in the criteria for classification of TLS[21]. But in this study there is no patient found with hyperkalemia and only1 (2.6%) patient had hypokalemia along with TLS, but there were other causes of hypokalemia related with leukemic patients e.g decreased potassium intake, gastrointestinal loss, vomiting and diarrhea as a complication of chemotherapy and several nephrotoxic drugs causing potassium loss and hypokalemia. Steroids as a part of chemotherapeutic regimen producing their mineralocorticoid effect can also causehypokalemia[25].

Conclusion

The results of the current study showed that there was an association of biochemical derangements with TLS in making the diagnosis of TLS by using the Cairo bishop criteria as a diagnostic tool and prompt diagnosis of TLS with the help of these biochemical derangements will help to reduce the mortality and morbidity in malignant patients, who received chemotherapy, but prophylactic therapy had a strong impact on patient outcome therefore decreasing the frequency of TLS.

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