Original Article

Tumour Lysis Syndrome in Haematological Malignancies

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ABSTRACT

OBJECTIVES: This study was conducted to determine the frequency of tumor lysis syndrome (TLS) in haematological malignancies.

MATERIALS AND METHODS: This descriptive study was conducted at Liaquat National Post-graduate Medical Centre from October 2005 to April 2006 over a period of six months. Total 50 patients with diagnosed haematological malignancies were included in the study and data were collected by non-probability convenient sampling. Patients pretreated for their malignancy were excluded from the study. Venous samples for serum uric acid, LDH, phosphorus, calcium, potassium and creatinine were collected on admission, before starting chemotherapy and then for four days after starting the chemotherapy. All patients received adequate hydration, allopurinol and induction chemotherapy. Data were analysed by statistical package for social sciences (SPSS) version16.0.

RESULTS: Out of 50 patients 10 fulfilled the criteria for TLS. Six patients developed laboratory tumor lysis syndrome (LTLS), whereas 4 developed clinical tumourlysis syndrome.Acute renal failure was observed in 4 out of 10 patients. Overall 3 patients died because of TLS. Hyperuricaemia and lactate dehydrogenase above 2000 IU were the most prominent findings in patients with TLS.

CONCLUSION: It is concluded that 20% of the patients developed TLS (including both laboratory and clinical TLS and despite all measures of prevention it can occur and result in devastating clinical effects.

KEYWORDS: Tumor lysis syndrome, hyperuricaemia, hyperphosphataemia, hypocalcaemia, acute renal failure.

INTRODUCTION

The tumorlysis syndrome (TLS) is the most common disease-related emergency encountered by physicians caring for children or adults with hematologic cancers.[1-3] Clinically significant TLS occurs typically after initiation of cancer treatment but spontaneous TLS unrelated to cancer treatment has also been documented.[4]The tumor lysis syndrome occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures and death due to multiorgan failure.[5]

There is lack of relevant local data for comparison after a thorough search in Pub-Med, E-Medicine and Google. Whereas search for international literature revealed that the most commonly referenced percentages are from Hande and Garrow's 1993, who reported the 42%incidence of tumourlysis syndrome, whereas the incidence of clinically significant TLS was only 6% in the same population.[6]A similar occurrence rate has been demonstrated in pediatric patients. Wossman et al reported the incidence of TLS to be 26.4% in children with B-cell acute lymphoblastic leukemia.[7]

The clinically relevant definition of TLS was developed by Cairo and Bishop [8].

DEFINITION OF LABORATORY TUMOUR LYSIS SYNDROME (LTLS)

- Uric acid more than 476 mmol/L or 25% increase from baseline.
- Potassium more than 6.0 mmol/L or 25% increase from baseline.
- Phosphorus more than 2.1 mmol/ in children or more than 1.45 mmol/L in adults or 25% increase from baseline.
- Calcium less than 1.75 mmol/L or 25% decrease from baseline

Laboratory tumourlysis syndrome (LTLS) is defined as either a 25% change of level above or below normal, as defined above, for any two or more serum values of given biochemical markers within 3 days before or 7 days after the initiation of chemotherapy(+/- alkalinization) and a hypouricaemic agent.

DEFINITION OF CLINICAL TUMOUR LYSIS SYNDROME (CTLS)

1. Creatinine more than 1.5 times upper limit of nor-

mal (age more than 12 years or age adjusted)
2. Cardiac arrhythmia/sudden death
3. Seizure

Clinical tumourlysis syndrome is labelled once there is LTLS in addition to one or more of the above-mentioned criteria.

Prevalence of TLS varies among different malignancies and there is no age or sex predilection. The risk is influenced by a number of characteristics including the type of malignancy, tumour burden, serum lactate dehydrogenase (LDH) levels, degree of involvement of the bone marrow and sensitivity of tumour to chemotherapy.[9-11]

Low urine output and preexisting hyperuricaemia or renal insufficiency are host related risk factors[9]for its development.TLS is a potentially fatal disease occurring spontaneously in patients with very aggressive haematologic cancers, such as Burkitt's lymphoma[10]and acute lymphoblastic leukaemia[11] (ALL), but it is also observed after the initiation of chemotherapy in less aggressive cancers such as diffuse large B cell lymphoma.[12-14]Some other haematological malignancies are also associated with TLS, including chronic lymphocytic leukaemia (CLL),acute myeloid leukaemia(AML) , multiple myeloma and isolated plasmacytomas.[15,16]

In addition there have been a few reports of TLS in low and intermediate grade non-Hodgkin's lymphomas with high proliferation rates and responsive to chemotherapyin addition to Hodgkin's disease, chronic myeloid leukaemia in blast crisis and myelopropliferative disorders.[17] It has been reported to be present in solid tumours.[18]

TLS is also associated with a variety of treatment regimens, including chemotherapy, immunotherapy ,hormonal treatment,radiation therapy,anaesthesia and surgery.[14,19,20] Various chemotherapeutic drugs have been implicated including corticosteroidsand hydroxyurea.[21] The identification of patients at risk for the development of TLS is the most important aspect of management so that prophylactic measures can be started prior to the initiation of therapy.

The purpose of this study is to determine the frequency of TLS in patients with various haematological malignancies.This will be helpful in early identification of patient at increased risk of this serious complication, which can occur in all types of haematological malignancies, in order to initiate appropriate prophylactic and therapeutic measures for its prevention as the data available are not showing any previous related study.

MATERIAL AND METHODS

This descriptive observational study was conducted at Haematology-Oncology Ward, Liaquat National Hospital Karachi, which is a tertiary care hospital, from 25th October 2005 to 24th April 2006. All consecutive patients presented with tissue diagnosis of haematological malignancies were included in the study. However, patients who had already been under treatment for malignancies and those patients who received drugs that may affect metabolic status were not included in the study.

During the six month study period 55 cases of haematological malignancies were presented in the ward but 5 of them were not selected for study because 3 patients already had received chemotherapy at some other hospital and 2 were on ACE inhibitors, which may cause hyperleukaemia. Therefore total 50 patients were included in the study.

After obtaining the informed consent, clinical history was taken and physical examination was performed. Baseline electrocardiography of each patient was recorded at presentation and was repeated if patient developed any symptoms or noticed to have arrhythmia.

Venous blood samples were drawn in EDTA tube for total leucocyte count (TLC) and were analyzed on Sysmex analyzer.Venous blood samples were drawn in lithium heparin coated vacutainers to determine the levels of serum phosphate, potassium, uric acid, creatinine, calcium, albumin andserum lactate dehydragenase (LDH) at presentation and then were checked daily from the day before starting chemotherapy (day 0) up to 4th post chemotherapy day (day 4).These samples were run on NOVA biomedical-4 automated analyzer for serum potassium and on Hitachi 911 automatic analyzer for serum uric acid, creatinine, calcium, phosphate, albumin and LDH.

All patients received hydration and allopurinol therapy once they got admitted and were started with induction chemotherapy.All patients with acute lymphoblastic leukaemia (ALL) received chemotherapy including vincristine, adriamycin, asparginase and prednisone.All patients with acute myeloid leukaemia (AML) received daunorubicin and cytosine arabinoside except patients with acute promyelocytic leukaemia who were offered All-Trans-Retinoic-Acid (ATRA) and Idarubicin.All patients with non-Hodgkins Lymphoma (NHL) received CHOP regimen (including cyclophosphamide, adriamycin, vincristine and prednisone).Patients with Hodgkin's disease (HD) received ABVD (adriamycin, bleomycin, vinblastine and dacarbazine).Patients with chronic myeloid leukaemia (CML) were started on hydroxyurea.

Data were analysed by statistical package for social sciences (SPSS) version 16.0 and relevant descriptive statistics were calculated.Frequency and percentages were computed for presentation of qualitative response variables of the study e.g.TLS, LTLS and

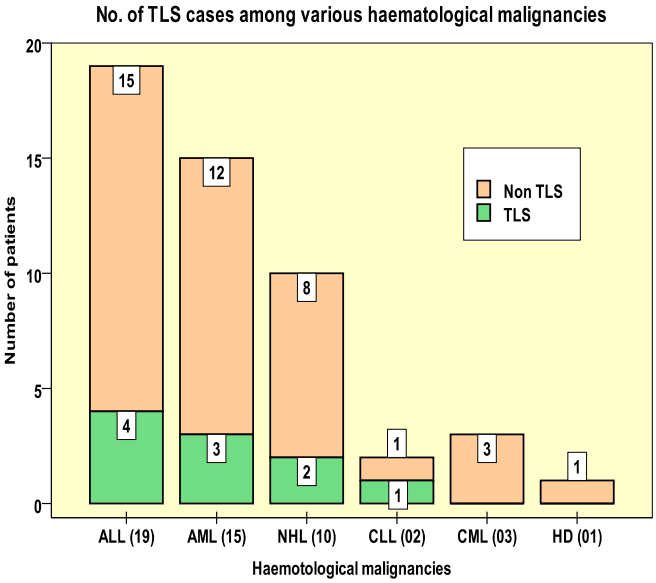
CTLS.Quantitative variables like serum uric acid, calcium, potassium, phosphate, creatinine and LDH are presented with mean and Standard Deviation.Independent sample t–test was used to compare mean difference between patients with TLS and those without TLS for quantitative variables like TLC, serum uric acid, calcium, potassium, phosphate, creatinine and LDH.P value 0.05 or less was considered as significant.

RESULTS

Among 50 patients, 31 were males and 19 were females with mean age of 43±5 years. Total 10 (20%) patients found to have TLS **(Figure I)**. Six (60%) cases were of laboratory TLS and 4 (40%) were of clinical TLS. Two (20%) developed TLS spontaneously i.e. before starting chemotherapy. Biochemical parameters of study population are detailed in **Table I**, whereas frequency of complications in TLS patients is detailed in **Table II**.

Hyperuricaemiawas present in 20 (40%) cases of haematological malignancies and in all 10 (100%) TLS cases. LDH levels ≥2000-IU was found in 11 (22%) cases of haematological cases and 8 of these patients developed TLS. Three (6%) patients of haematological malignancies died due to TLS related complications.

FIGURE I: TLS AMONG VARIOUS HAEMATOLOGICAL MALIGNANCIES



ALL=Acute lymohoblasticleukaemia
AML= Acute myeloid leukaemia
NHL= Non hodgkins lymphoma
CLL=Chronic lymphocytic leukaemia
CML=Chronic myeloid leukaemia
HD= Hodgkins disease

FIGURE II:

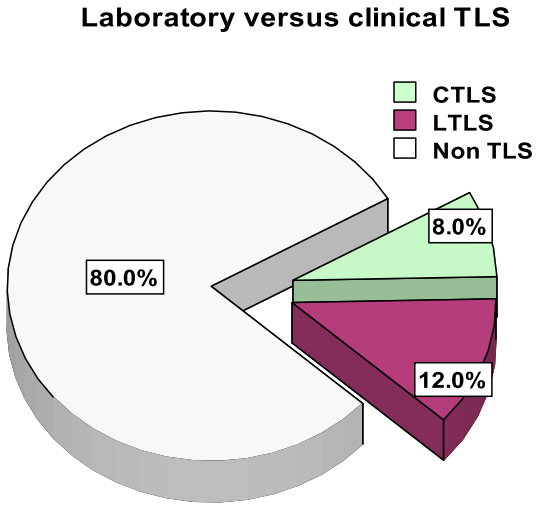


TABLE I: LABORATORY PARAMETERS IN PATIENTS WITH AND WITHOUT TLS

Laboratory parameters	Non TLS Group N=40	TLS Group N=10	P value
Total Leucocyte Count (10^9/L)	45.47 +/- 59.005	100.8 +/- 75.04	*0.015
LDH (IU)	1797 +/- 3815	9204 +/- 16899	*0.0005
Serum Creatinine (Mg/dl)	0.856 +/- 0.4815	4.140 +/- 2.953	*0.0005
Serum Potassium (mEq/ L)	4.258+/- 0.6003	4.440+/1.5 094	0.346
Serum Uric acid (mg/dl)	6.004 +/- 3.8133	17.86 +/- 6.145	*0.0005
Serum Phosphate (mg/dL)	3.621 +/- 1.847	8.300 +/- 3.81	*0.0005
Corrected Serum Calcium (mg/ dL)	9.308 +/- 1.1283	8.370 +/- 1.24	*0.026

Values are expressed as mean±SD
*=significant

TABLE II: COMPLICATIONS OBSERVED IN PATIENTS WITH TUMOURLYSIS SYNDROME (n=10)

Complications	Frequency (%)
Acute renal failure	4 (40)
Cardiac arrhythmia	2 (20)
Seizure	1 (10)
Death	3 (30)

DISCUSSION

TLS occurs in 5-20% of cancer patients, it represents a serious complication that can potentially lead to death. It is therefore, mandatory to recognize risk factors, and to set up prophylaxis and treatment of TLS in order to offer patients the opportunity to receive an adequate therapy for neoplasm.[22]

We compared our study with data published in the international literature.

Unfortunately we lack relevant local data for comparison after a thorough search in Pub-Med, E-Medicine and Google.

TLS occurred in 20% of our patients, 6 out of them had laboratory tumourlysis syndrome and 4 patients developed clinical tumourlysis syndrome which means 12% and 8% for each category respectively.

While searching for international literature we found that TLS was first reported almost 80 years ago, but its incidence remains ill-defined.[10] The most commonly referenced percentages are from Hande and Garrow's 1993, who reported the incidence of tumourlysis syndrome identified through serial measurements of laboratory values to be 42%, whereas the incidence of clinically significant TLS was only 6% in the same population.[6] A similar occurrence rate has been demonstrated in pediatric patients. Wossman et al reported the incidence of TLS to be 26.4% in children with B-cell acute lymphoblastic leukemia.[7] Reasons for the inability to precisely define TLS incidence include variations in defining the syndrome, variations in anticipating and studying its development in selected patient population, and failure to report all occurrences.[8]

However in another study the incidence of TLS was reported as of 6.1% in patients diagnosed to have NHL.[17]In present study 4% patients had spontaneous TLS where as 16% developed TLS after chemotherapy. As far as we know, the largest single center study conducted to analyze the incidence and risk factors for TLS in patients with AML reported 5% incidence of CTLS, similar to that previously reported in patients with AML[16].

A pan European retrospective chart review identified TLS in 3.4%, 5.2% and 6.1% patients with AML, ALL and NHL respectively with an overall mortality of 0.9% for all patients and 17.5% for patients who developed TLS, whereas 1.9% of the global population was observed to die as a result of TLS related Complications[23].

Difference in incidence rates reported here can be attributed to several factors, such as application of slightly different criteria to recognize TLS, difference in study population, age, underlying malignancy and stage of disease at the time of diagnosis. Higher incidence of clinical TLS in our study compared with the other studies can be result of advanced stage of the disease at time of diagnosis, late arrival of patients to a concerned specialty, lack of awareness on the part of referring as well as treating clinician, underlying malignancy, and pre- existing renal insufficiency. The incidence rates of complications observed in the study were compared with the incidence rates reported in a study of 755 patients conducted to find out incidence of hyperuricaemia and TLS in patients with leukaemia and lymphoma. The study reported that overall 73% patients experienced significant symptomatic complications of the syndrome.

The renal failure seemed to occur because of acute uric acid nephropathy as patients in the sample had increased uric acid production and hyperuricosuria resulting from high tumor cell turnover rate. Search through the literature has shown a considerably reduced incidence of significant post-treatment hyperuricemia and a predominance of hyperphosphatemia as the most common laboratory abnormalities associated with post-treatment ARF. In a series of 16 patients who had sustained a nephropathy because of acute hyperuricaemia, four patients developed the syndrome before starting treatment.[24]

Another study identified 10 out of 926 ARF patients with hyperuricaemia induced nephropathy in spontaneous TLS (before even initiation of treatment). Among them 45% of patients with TLS had ARF, 13% of patients had cardiac arrhythmias and 15% patients died due to TLS.[25]Literature search reveals few case reports of TLS developing spontaneously.[23,26]No proper study has been conducted to find out the incidence of spontaneous form of TLS.

Acute TLS is possibly the most significant cause of acute renal failure in patients with malignancies.They exhibit renal insufficiency ranging from 5% to 30% during initial therapy and has been reported in literature in haematological malignancies. About 15% to 30% of these patients required dialysis.This statement can be supported by another study of 1192 patients with NHL or B-cell ALL, treated between 1990 and 1997,63 (5.3%) patients suffered from impaired renal functions. Out of these, 25 (9.7%) underwent hemodialysis.[26]These results are compatible with our study

where renal failure has been found to be a significant complication of TLS.

Hyperuricaemia was the most common abnormality seen in this study (40%), which in turn is related to high tumour cell burden as indicated by high WBC count and increased LDH levels. Acute lymphoblastic leukaemia both B and T types and non-Hodgkin lymphoma like Burkitts lymphoma are commonly associated with hyperuricaemia and TLS. Since these conditions are associated with a heavy tumour burden, rapid cell turnover and high sensitivity to chemotherapy.[27]It occurs less frequently in chronic leukaemia.[25]Hyepruricemia had been reported as being the most consistent finding (38.7%) in patients with acute lymphocytic leukaemia in whom the study was conducted to determine electrolyte perturbations at diagnosis that may be a clue for renal damage in long-term period and the study related it to the above mentioned factors.

Another study described the incidence rate of 18.9% of hyperuricaemia and 5% of TLS, respectivelyin patients with acute leukemia and NHL in four European countries.[26]

Interestingly, a National Cancer Institute analysis of NHL and TLS correlated the risk of developing the syndrome with pretreatment LDH levels.[28]Indeed in our cases of TLS pretreatment LDH levels were remarkably high, probably reflecting the high tumour burden and proliferation fraction.

CONCLUSION AND RECOMMENDATIONS

It is indicated by the results of our study that in spite of available preventive measuresTLS can occur and result in significant morbidity and mortality. That is why, it is important to recognize those patients who are at risk for the development of complications or death secondary to TLS.

Tumourlysis syndrome is a life-threatening complication of malignancy. Early identification of patients at risk and prevention is of crucial importance. It is seen commonly after chemotherapy which initiates massive cell death and lysis of cell contents. During treatment such patients should be observed and monitored closely. Uric acid, LDH, creatinine, potassium, calcium and phosphate levels should be measured at the time of presentation and thereafter frequently in order to diagnose LTLS and prevent CTLS, which is potentially fatal. These biochemical abnormalities can be concurrently exacerbated by renal failure.

It is recommended that prompt recognition and aggressive management of this life threatening complication by aggressive fluid and electrolyte management is essential to treat this condition which can occur in almost all haematological malignancies.

Biochemical changes occurring should be corrected and monitored to prevent serious complications such as seizures,cardiac arrhythmias,renal failure and death.

It is also recommended that junior doctors undergoing training in tertiary care centres should be mandatorily trained for early recognition and management of this serious but preventable complication in their subsequent practice.

Moreover the sample size was too small, and we recommend to conduct a larger multi-centric study in various tertiary referral centres of Pakistan to get a clear incidence of tumor lysis syndrome in haematological-malignancies in Pakistan.

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