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Review Article

TUMOR LYSIS SYNDROME IN PAEDIATRIC CANCER PATIENTS

MORSHED AKMA[1], ISLAM S[2]

Abstract

Introduction: Tumor lysis syndrome (TLS) is a common complication of malignancies and can result in renal failure or death.

Review: In paediatric tumor with a high proliferative rate and relatively large mass and a high sensitivity to cytotoxic agents, beging of therapy often results in the rapid release of intracellular metabolic products of proteins and nucleic acids into the bloodstream. Raised concentrations of uric acid, phosphates, potassium and urea can overwhelm the body's homeostatic mechanisms to excrete these materials and result in the clinical spectrum associated with TLS. Clinical features include gastrointestinal disturbances, neuromuscular effects, cardiovascular complications, acute renal failure and death. The incidence of clinical TLS is approximately 6% for acute leukemias and 10% for lymphomas. Pediatric cancers are the leading cause of death by disease in children. The most common pediatric cancers include the leukemias, lymphoma, Wilms' tumor and neuroblastoma. Thus, TLS prevention and treatment is a multidisciplinary approach involving the collaboration of medical oncologists/ hematologists and nephrologists has role for optimal patient outcomes. Rehydration is fundamental in the management of TLS. For hyperuricemia we may use allopurinol.

Conclusion: The early diagnosis and treatment of metabolic abnormalities prevents the severe complications of tumor lysis syndrome.

Key words: Tumor Lysis syndrome, Children, Cancer

Introduction

Tumor lysis syndrome arises due to the rapid release of intracellular metabolites (such as phosphorous, potassium and uric acid) from necrotic tumor cells in quantities that exceed the excretory capacity of the kidneys. TLS common **in** patients with high tumor burden, bulky tumor, rapidly proliferating tumors, in highly chemo and radiotherapy sensitive disease, especially with Burkitt or Burkitt-like lymphoma, B-cell acute lymphoblastic leukemia and T-cell leukemia or lymphoma.[1] Significant cell death and release of intracellular ions and may result in the following metabolic complications before starting chemotherapy:[2]

- Hyperuricemia
- Hyperkalemia
- Hyperphosphatemia
- Hypocalcemia
- Renal insufficiency/failure

Cairo and Bishop[3] formulated a commonly usedclassiûcationsystemforTLS.Thissystem deûnes LTLS when two or more of the following abnormalities are met within 3 days before or 7 days after the initiation of chemotherapy:

1) 25% decrease from baseline in serum calcium, and/or
2) 25% increase frombaseline intheserumvalues ofuricacid, potassium, or phosphorous.

1. Prof. AKM Amirul Morshed, Professor and Head, Dept. of Paediatric Haematology & Oncology, Dhaka Medical College Hospital.
2. Prof. Shahnoor Islam, Professor, Dept. of Paediatric Surgery, Dhaka Medical College Hospital

Correspondence: Prof. AKM Amirul Morshed, Professor and Head, Department of Paediatric Haematology & Oncology, Dhaka Medical College Hospital, Dhaka E-mail: amirulmorshed63 @gmail.com

Risk factors:[1,4]

Type of Cancer	RU		
	High	Intermediate	Low
NHL	Burkitt, lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBCe"100,000/mm^3	WBC 50,000- 100,000/mm^3	WBCd"50,000/mm^3
AML	WBCe"50,000/mm^3	WBC 10,000-50,000/mm^3	WBCd"10,000/mm^3
CLL		WBC 10,000-100,000/mm^3 Tx w/fludarabine	WBCd"10,000/mm^3
Other hematologic malignancies (including CML and multiple myeloma) and solid		Rapid proliferation with expected rapid response to therapy	Remainder of patients

Pathophysiology of TLS

Lysis of cancer cells releases DNA, phosphate, potassium, and cytokines. DNA released from the lysed cells is metabolized into adenosine and guanosine, both of which are converted into xanthine. Xanthine is then oxidized by xanthine oxidase, leading to the production of uric acid, which is excreted by the kidneys. When the accumulation of phosphate, potassium, xanthine, or uric acid is more rapid than excretion, the tumor lysis syndrome develops. Cytokines cause hypotension, inflammation, and acute kidney injury, which increase the risk for the tumor lysis syndrome. Acute kidney injury increases the risk of the tumor lysis syndrome by reducing the ability of the kidneys to excrete uric acid, xanthine, phosphate, and potassium.[5,6]

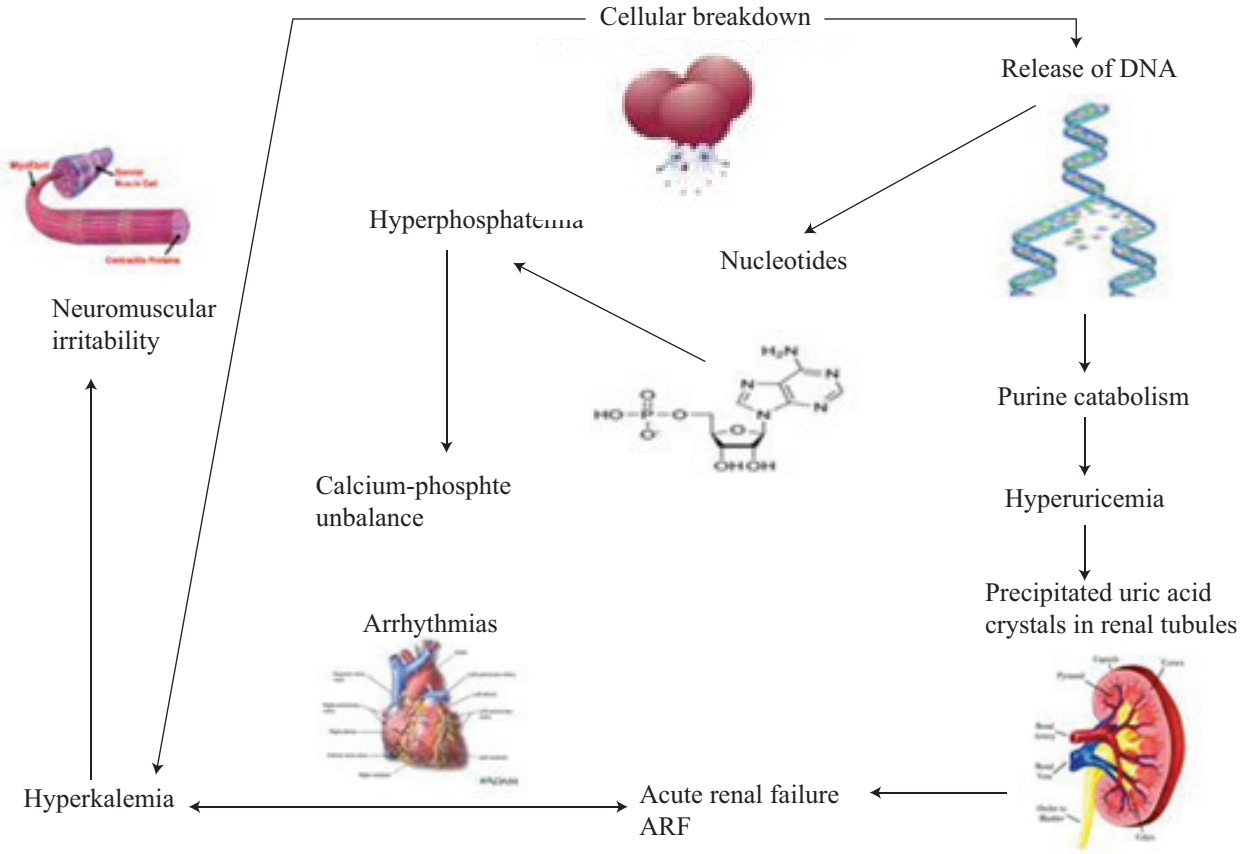

Fig.-1: *Showing the pathogenesis of TLS*[5]

Manifestations of TLS

Usually occurs within 24-48 hours after initiation of chemotherapy and may persist for 5-7 days post therapy. May occur as early as 6 hours post chemotherapy administration. TLS of two types 1. Laboratory Tumor Lysis Syndrome (LTLS) 2. Clinical Tumor Lysis Syndrome (CTLS).[4,] Organ specific manifestations are as follows -cardiac: bradycardia, heart block, cardiac arrest. Neuromuscular-weakness, lethargy, cramping, tetany, chvostek's sign, trousseau's sign and convulsions. Renal manifestations are oliguria, renal insufficiency, flank pain, weight gain, edema, renal failure. Gastrointestinal: nausea, vomiting, diarrhea and constipation.[7,8,,9]

Hyperuricemia [10]

Results from tumor cell destruction
Most common signs and symptoms
Nausea and vomiting
Azotemia
Oliguria
Anuria
Decreased urine pH
Uric acid crystals found in urinalysis

Hyperphostaemia[10]

Most common signs and symptoms
Hypocalcemia
Renal failure
Azotemia
Ologuria
Anuria
Hypertention
Edema

Hyperkalemia[10]

Result from rapid destruction of cells
Most common signs and symptoms
- Weakness
- Twitching
- Increased bowel sounds
- Nausea
- Diarrhea
- Cardiac abnormality
- EKG changes
  - Peaked t waves
  - Flat p waves
  - Wide QRS complexes
  - Bradycardia
  - Ventricular tachycardia
  - Ventricular fibrillation

Hypocalcemia[10]

Results from hyperphosphatemia and
inverse relationship of calcium and phosphorous
Most common signs and symptoms
Neuromuscular signs and symptoms
- Tetany
- Twitching
- Paresthesias
- Seizures
- GI Symptoms
- Diarrhea
- EKG changes
  - Prolonged QT
  - Inverted T waves
  - Ventricular dysrhythmias
  - Heart block
  - Cardiac arrest

Diagnostic Criteria for Laboratory TLS (LTLS) & Clinical TLS (CTLS)[2,4]

LTLS:

The presence of two or more abnormal serum values at presentation. 1. Uric acid- >8 mg/dl 2. Potassium- >6 mg/dl, 3. Phosphate- >2.1 mmol/L 4. Calcium- <1.75 mmol/L) or Change in serum values by 25% within 3 days before or 7 days after initiation of therapy.

CTLS:

Presence of LTLS and one or more of the following clinical complications: Renal insufficiency, Cardiac arrhythmias, Seizures or Sudden death

Recognition of risk factors, close monitoring and appropriate preventative intervention are vital in managing TLS.

If not successfully treated, tumor lysis syndrome can result in cardiac arrhythmias, renal failure, seizures, coma, disseminated intravascular coagulation (DIC) and death.

Investigations for TLS[1]

1.Complete blood count 2.S. Electrolytes should include Sodium (Na), Potassium (K), Phosphate (P), Calcium (Ca), Magnesium (Mg) 3. BUN5. Uric acid 7. S. LDH

Management[11,12]

Aggressive hydration	Usually 2.5 – 3 lit/m2
Diuresis	Furosemide 0.5–1 mg/kg/dose, Mannitol 0.5 g/kg can be used
Transfusion	Platelet transfusion to keep platelet count over 20,000/mm^3 Avoid packed RBC transfusions,
Chemotherapy	Chemotherapy should be started when patient is stabilized and has adequate urine Output
Monitor	Monitor Electrolytes; calcium, phosphorus, uric acid, BUN, creatinine every 6 hours Complete blood counts every 12 hours. Urine output, pH and specific gravity every 6 hours
Metabolic Abnormalities	Accordingly
Dialysis	
Imaging	Brain CT with contrast if no renal insufficiency in the presence of neurologic symptoms or signs.

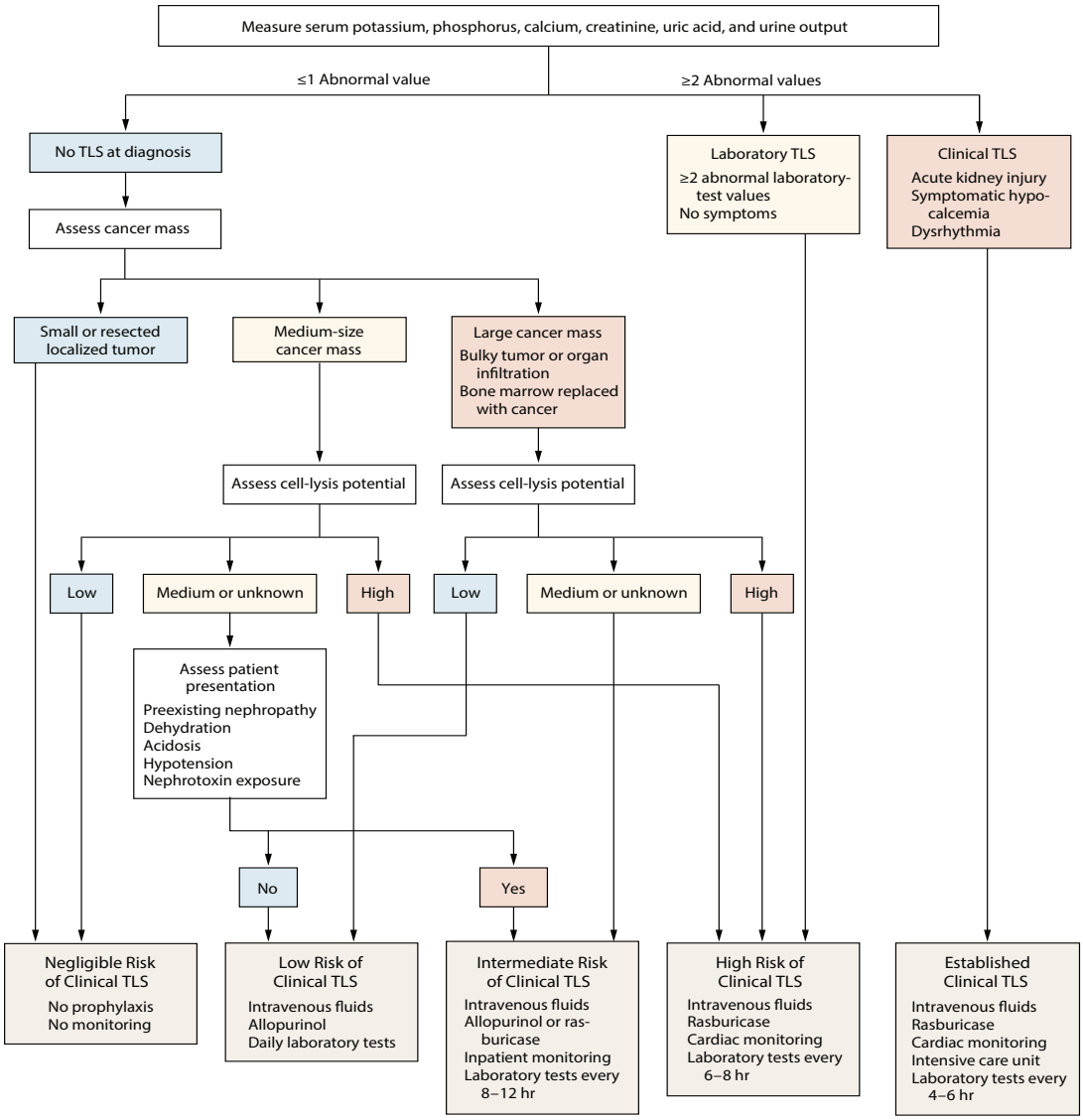

Fig.-2: *Guideline for management of TLS*[5]

Identify patients at risk and monitor for all electrolyte abnormalities. Hydration before chemotherapy and administer allopurinol which decrease uric acid levels by interfering with purine metabolism through the inhibition of the enzyme xanthine oxidase that is essential for the conversion of nucleic acids to uric acid.[4,13,14,] Rasburicase, a recombinant urate oxidase may used to reduces the uric acid pool. Unlike allopurinol, rasburicase will reduce pre-existing uric acid. Serum urate concentrations have been shown to decrease more rapidly after rasburicase than after allopurinol administration.[14]

To reduce hyperkalemia kayexalate with sorbitol, calcium gluconate , sodium bicarbonate, hypertonic dextrose and regular insulin, Albuterol (Ventolin) or another beta stimulant and/or dialysis may be applied.Limitation of phosphate intake, enhancement of renal excretion of phosphate and enhancement of urinary losses through forced saline diuresis to reduce hyperphosphatemia. Intravenous infusion of calcium gluconate slowly to combat with hypocalcemia. Avoid nephrotoxic medications and avoid agents which block tubular reabsorption of uric acid like Aspirin, Probencid, Thiazide diuretics, Radiographic contrast containing iodine.[4,13,14]

Measure serum potassium, phosphorus calium creatinine uric acid and urine output

Dialysis is required in 1.Presence of hyper-phosphatemia (>6 mg/dL) and hypercalcemia. 2. An estimated glomerular filtration rate (GFR) less than 50%. 3. Persistent hyperkalemia with QR interval widening and/or level exceeding 6 mEq/LS 4. Severe metabolic acidosis. 5. Volume overload unresponsive to diuretic therapy 6.Anuria and overt uremic symptoms (i.e. encephalopathy). 7. Severe symptomatic hypocalcaemia 8. Congestive heart failure. 9. Severe hyperuricemia

Nursing intervention[15,16]

Symptom management

Maintenance of fluid status

Review of systems like cardiac, renal, neurologic. Gastrointestinal system.

Monitor weights at least daily

Daily EKG's

Monitor for altered level of consciousness

Strict I&O

Check pH of urine with each void, goal is to keep pH >7.0

Monitor for signs and symptoms of nausea and vomiting, administer antiemetics as ordered

Management of Tumor Lysis Syndrome of paediatric cancer is a multidisciplinary approach. Combined effort of paediatric Oncologist, Paediatric nephrologist, Critical care specialist, Paediatric surgeon and other supporting staffs are essential for successful management of TLS.

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