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Characteristics of tumor lysis syndrome in pediatric oncology patients. A single-center observational study.

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Abstract

Introduction: Tumor lysis syndrome (TLS) is an oncological emergency that results in metabolic alterations, causing clinical manifestations and biochemical disorders that endanger patients' lives. The objective of the present study was to identify the clinical, laboratory, and treatment characteristics of TLSs in pediatric oncology patients at the SOLCA-Cuenca Cancer Institute from 2010–2020.

Materials and methods: In this study, the characteristics of TLS were identified in pediatric oncology patients at the SOLCA-Cuenca Cancer Institute from 2010 to 2020 through a descriptive observational study.

Results: A total of 463 medical records were included. TLSs were associated with a frequency of 5.61%, with a predominance of males (57.7%) and a mean age of 7 ± 1.29 years. The most common clinical presentation was dehydration with nausea, vomiting, and diarrhea (57.7%). The most frequent laboratory alterations were hyperuricemia and hypocalcemia, with 76.9% and 73.1%, respectively. The oncological diagnosis was acute lymphoblastic leukemia (ALL) in most patients (61.5%). The pillars of treatment were hyperhydration and allopurinol, used in 100% and 80.8%, respectively.

Conclusion: TLSs more frequently affect men with a diagnosis of leukemia, digestive clinical manifestations, or laboratory alterations (hyperuricemia and hypocalcemia). The treatment used was effective and based on what the medical literature recommended.

Keywords:

MeSH: Allopurinol; Tumor Lysis Syndrome; Organism Hydration Status; Leukemia; Child.

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Introduction

Tumor lysis syndrome (TLS) is an oncological emergency found in children or adults with cancers, especially hematological malignancies (acute leukemia and non-Hodgkin lymphoma) [1]. Generally, it occurs at the beginning of chemotherapy, but it can occur exceptionally after the spontaneous necrosis of some tumors in the absence of antitumor treatment [2]. Its incidence varies from 3% to 26%, depending on several factors, such as the type of tumor and treatment received, and its mortality varies between 29% and 79%. Both morbidity and mortality can be reduced by timely diagnosis and treatment [3, 4].

TLSs cause metabolic alterations and clinical and biochemical manifestations that result from the massive release of intracellular substances into the extracellular space caused by the rapid destruction of tumor cells [5]. Its presentation may be clinical syndrome (dehydration, nausea, vomiting, arrhythmias, neurological complications, and ARF) or only a change in laboratory values. The latter is more common and is defined by the appearance, in a period of 24 hours (h), of two or more alterations in electrolytes (hyperkalemia, hyperphosphatemia, hypocalcemia) or hyperuricemia three days before or up to seven days after the onset of chemotherapy treatment [4, 6], so it can be called spontaneous TLS or chemotherapy-induced TLS [7].

The Cairo-Bishop and Howard criteria are used for diagnosis and grading, for which clinical and laboratory definitions are presented, and patients are stratified into V possible grades [1, 7]. Prevention includes early identification of high-risk patients, laboratory monitoring, adequate hydration, and uricosurics. Adequate hyperhydration is the primary therapeutic measure used to promote the excretion of uric acid and phosphates. Hypouricemic agents such as allopurinol may be effective [3].

Therefore, identifying clinical, laboratory, and treatment characteristics and the frequency and type of SLT (primary or secondary) is fundamental for optimal and timely management.

Our country does not have updated data on this pathology, which motivated us to conduct this research project to obtain local data on the frequency, characteristics, and treatment approach for this syndrome.

The research objective was to identify the clinical, laboratory, and treatment characteristics of TLSs in pediatric oncology patients at the SOLCA-Cuenca Cancer Institute from 2010 to 2020.

Materials and methods

Study design

This research was observational and descriptive; the source was retrospective.

Scenery

The study was conducted in the pediatric oncology service of the SOLCA Cancer Institute in Cuenca, province of Azuay. The study period was from January 1, 2010, to December 31, 2020.

Participants

All medical records of pediatric oncology patients treated during the study were included. Only complete medical records were included.

Universe and sample

The sample was nonprobabilistic since all incidental cases from the study period were included.

Variables

Demographic variables were recorded: age and sex.

- **Clinical characteristics**: Dehydration, nausea, vomiting, diarrhea, arrhythmias and seizures. Presence of the following conditions:
  - Oliguric or anuric acute renal failure
  - Tetany, paresthesia, or muscle spasm.
  - Arterial hypotension
  - Cardiogenic shock
  - Sudden death
- **Laboratory features**
  - Potassium ≥ 6.0 mmol/l or more than a 25% increase compared to baseline.
  - Phosphorus ≥ 1.45 mmol/l, a 25% increase from baseline.
  - Calcium intake ≤ 1.75 mmol/l or a 25% decrease compared to baseline.
  - Uric acid ≥ 8 mg/dl (476 mmol/l) or a 25% increase compared to baseline.
  - Creatinine ≥ 1.5 ULN
  - Leukocytes: ≤ 10,000/mm3, between 10,000 and 50,000, and ≥ 50,000/mm3
  - LDH: greater than 400 U/l
  - TGO: greater than 50 U/l
- **Type of cancer**
  - Acute lymphoblastic leukemia
  - Burkitt type non-Hodgkin lymphoma
  - Acute myeloblastic leukemia
  - Chronic lymphoblastic leukemia
- **Others**
  - TLS treatment
  - Hyperhydration
  - Allopurinol
  - Rasburicase
  - Diuretics

Method

Medical records were observed, and data were collected from the electronic records. The data were ordered, classified, and tabulated for subsequent analysis. The results are presented in frequency and percentage tables, and measures of central tendency (mean) and dispersion (standard deviation) were calculated for the continuous variables, with the results being presented in tables according to the variable type.

Statistical analysis

A noninferential analysis was performed. Qualitative variables are presented as the frequency and percentage. A 95% confidence interval is presented for a proportion of the most relevant prevalences. The scale variables are presented as the average and standard deviation.

Results

Presentation according to SLT frequency

A total of 463 medical records of pediatric oncology patients were analyzed, and 26 (5.61%) patients presented with TLS, either spontaneously or after starting chemotherapy. The population's 95% confidence interval (CI) ranged from 3.51% to 7.771%.

Presentation according to sociodemographic characteristics

A total of 57.7% of the patients were male. The most representative age was between 5 and 11 years, representing 30.8% of the participants, with a mean age of 7 ± 1.29 years. A minimum age of 6 months and a maximum of 16 years and five months were observed (Table 1).

Clinical characteristics

There were 15 symptomatic patients (57.7%) and 11 asymptomatic patients (42.3%). The main symptoms were gastrointestinal (Table 2).

Table 1. Presentation according to the sociodemographic variables of the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Demographic information		No.	%
Sex	Male	15	57.7
	Female	11	42.3
Age	0 – 364 days	4	15.4
	1 – 1 year 364 days	3	11.5
	2 – 4 years 364 days	7	26.9
	5 – 11 years, 364 days	8	30.8
	12 – 17 years, 364 days	4	15.5

Table 2. Presentation according to clinical manifestations of the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Clinical manifestations	No.	%
Dehydration	15	57.7
Hypotension	13	50.0
Acute kidney failure	6	23.1
Tetany and spasms	5	19.2
Seizures	4	15.4
Shock	4	15.4
Cardiac arrhythmias	1	3.8
Death	0	0

The most frequent symptom was dehydration, nausea, vomiting, and diarrhea (57.7%).

Cardiac arrhythmias were present in one patient during treatment, while 4 (15.4%) patients had seizures. Six patients had ARF, which represented 23.1%. A total of 19.2% had tetany, spasms, or muscle alterations. Hypotension was present in half of the patients. Four patients experienced shock, representing 15.4%; however, no patients died due to TLS.

Presentation according to hydroelectrolyte alterations

The most frequent alteration was hyperuricemia, which occurred in 20 (76.9%) patients; this frequency was much greater than the less frequent alteration, hyperkalemia, in 5 (19.2) patients (Table 3).

Table 3 . Hydroelectrolyte alterations in the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Variables	No	Yes	Mean ± SD	Minimum	Maximum
Hyperkalemia	21 (80.8%)	5 (19.2%)	4.37±0.96	2.9	6.9
Hyperphosphatemia	9 (34.6%)	17 (65.4%)	1.35±0.48	1.0	13.8
Hypocalcemia	7 (26.9%)	19 (73.1%)	1.27±0.45	2.1	11.0

Hyperuricemia	6 (23.1%)	20 (76.9%)	8.98±3.62	3.0	18.0

Presentation according to risk factors

Only 6 (23.1%) patients presented a creatinine elevation above 1.5, compared to the LDH alteration observed in most patients. Furthermore, hyperleukocytosis was present in more than half of the patients. Interestingly, GOT values were elevated in more patients than were GPT values (Table 4).

Table 4. Presentation of the risk factors in the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Variables	No	Yes	Mean ± SD	Minimum	Maximum
Creatinine ≥1.5	20 (76.9%)	6 (23.1%)	1.19±0.98	0.31	3.70
Hyperleukocytosis	12 (46.2%)	14 (53.8%)	147,546 ± 222,505	1000	876,540
LDH ≥ 400	3 (11.5%)	23 (88.5%)	3487 ± 4031	100	15,470
TGO ≥ 40	8 (30.8%)	18 (69.2%)	236 ± 347	14	1,323
TGP ≥ 50	16 (61.5%)	10 (38.5%)	122±225	10	990

P value according to the type of cancer

In the present study, the type of cancer that presented the most cases of TLS was ALL, with 16 (61.5%) patients, followed by chronic myeloid leukemia and retinoblastoma, with 2 cases each. Additionally, TLSs were found in the following patients: Burkitt-type non-Hodgkin lymphoma, AML, peripheral T-cell lymphoma, malignant adrenal gland tumor, malignant kidney tumor, and hepatoblastoma (Table 5).

Table 5. Frequency according to the type of cancer in the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Type of Cancer	No.	%
Acute lymphoblastic leukemia	16	61.5
Chronic myeloid leukemia	2	7.6
Retinoblastoma	2	7.6
Others	6	22.8

Form of presentation of the TLS

Of the 26 pediatric oncology patients with TLSs, 15 (57.7%) patients presented spontaneously, while 11 (42.3%) presented with secondary syndrome, of which 1 (9.1%) occurred during the prephase. In contrast, in 10 (90.9%) patients, the disease manifested from day 0 to the seventh day of induction, with day 1 being the most common disease occurring, with 12 (46.2%) patients, followed by day 2, with 7 (26.9%) patients. (Table 6).

Table 6. Form of presentation of the TLS of the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

Form of presentation	No.	%
Primary (spontaneous) TLS	15	57.7
Secondary TLS	11	42.3

Patient characteristics according to the treatment used

All patients were observed to have hyperhydration during treatment. Allopurinol was used in 21 (80.8%) patients. However, rasburicase was not used in any of the patients. Diuretics were also administered to 18 patients (69.2%) (Table 7).

Table 7. Presentation of the frequency of treatment of the 26 patients with TLS from the SOLCA Cancer Institute, Cuenca, 2010 – 2020. Cuenca 2021.

TLS treatment	No.	%
Hyperhydration	26	100
Allopurinol	21	80.8
Rasburicase	0	0
Diuretics	18	69.2

Discussion

In the present study, 26 cases of TLS were observed in pediatric oncology patients, for an incidence of 5.61%, which was more frequent in males (57.7%) with a mean age of 7 ± 1.29 years. Compared with the results of a study called TLS in pediatric ALL in a tertiary care center carried out at the National Institute of Child Health in 2019 [8, 9], similarities were found in males, with a frequency of 57% and an age mean of 6.39 ± 3.08 years. Similarly, compared with the findings of another study titled TLS in children with hematological cancers (Pakistan) [10], these findings are consistent with our findings, in which a frequency of 67.2% of males and an overall mean age of 7.8 ± 4.1 years were reported.

The preference for the male sex is explained by the fact that hematological cancers are more common in men, and due to their physioanatomical characteristics, they predispose them to the presentation of TLSs. The age range of patients with this type of cancer was more common at 2 to 5 years, which explains the frequency of disease in our study [11].

The clinical presentation was found in 57.7% of the patients, with dehydration, nausea, vomiting, and diarrhea as the primary manifestations, 57.5% of whom agreed with the bibliographic data reviewed. Gastrointestinal manifestations, such as nausea, vomiting, and diarrhea, are commonly associated with electrolyte disturbances [12]. This gastrointestinal manifestation would explain why these variations affect the gastrointestinal system, leading to nausea, vomiting, and diarrhea that can lead to dehydration; this clinical picture is exacerbated by the effects associated with chemotherapy [13].

The most frequent laboratory alterations were hyperuricemia (76.9%), followed by hypocalcemia (73.1%), hyperphosphatemia (65.4%), and hyperkalemia (19.2%). In the study named Evaluation and Characterization of TLS before and after Chemotherapy in Pediatric Oncology Patients at Tikur Anbessa Specialized Hospital, Ethiopia, [14] it was reported that the most common laboratory abnormality was hyperuricemia followed by hyperkalemia about our study, the first biochemical alteration is coincidental; In other studies [10] they mention hyperphosphatemia and hypocalcemia as the most frequent biochemical alterations, so the presence of hypocalcemia observable in our study is among the first alterations according to the medical literature. This alteration is associated with hyperphosphatemia, which results in the precipitation of calcium in extraosseous tissues and bone. This vascular precipitation, accompanied by a state of malnutrition in cancer patients, poor intestinal calcium absorption, and renal alterations, leads to the presentation of hypocalcemia [15].

According to the risk factors, an 88.5% increase in LDH was evident, followed by the rise in GOT of 69.2%, similar to the study's findings by Naeem B. et al. [9], also indicated that a large portion of the patients had elevated LDH levels, which the high cell proliferation of the tumor can explain. According to M. García Bernal and I. Badell Serra, elevated LDH is very common in most of the cases studied so that this risk factor may be due to the lysis of tumor cells, the presence of hepatic infiltration and ineffective hematopoiesis [16].

ALL was the most common diagnosis (61.5% of TLSs), which is consistent with the findings of previous reports that TLSs are more frequently observed in patients diagnosed with lymphoproliferative syndromes such as ALL, Burkitt's lymphoma and AML [17]. In addition, ALL is the primary oncological diagnosis in pediatrics [18].

Regarding the form of TLS presentation observed, the most common was spontaneous or primary TLS (57.7%), while 42.3% presented with the secondary form, with day 1 of chemotherapy induction being the most common form with the highest number of cases. (46.2%). Therefore, when corroborating the abovementioned literature, it is agreed that the laboratory form of presentation predominates over the clinical form according to the Cairo and Bishop criteria. When comparing our results with the study by Micho H. et al. [14], in which 72.2% of the 18 patients studied had spontaneous TLSs and 27.8% had spontaneous TLSs induced by chemotherapy, our values agreed with said study; however, various case studies mention contrary results, which may be attributed to multiple factors, such as differences in the study population, the underlying malignancy and its stage, the age group, the late presentation of patients to the health center, the application of slightly different criteria to diagnose TLSs or even the type of medication applied to the oncological disease provided by the health institution. However, additional research is needed to determine the causes of this difference precisely [14].

The clinical application of allopurinol is based on hyperhydration treatment, followed by allopurinol treatment, which agrees with the available published data. According to the Clinical Practice Guidelines in Pediatrics from the Chilean Ministry of Health of 2018, hydration is fundamental to maintaining adequate diuresis and avoiding complications. Allopurinol is also recommended for patients at low or intermediate risk of developing TLS. However, when Rasburicase cannot access [19], this last drug is unavailable in our country, so allopurinol was chosen for further study. Investigating the use of this drug in our region is essential for improving the treatment and prognosis of patients.

The following points could summarize the possible contributions of this work: a) the lack of studies supporting management in pediatric oncology patients should be a cause of concern for the corresponding researchers; b) the correct application of diagnostic and therapeutic criteria contributes to better future results; and c) the use of allopurinol in conjunction with hyperhydration is a frequent finding in the studies analyzed where therapeutic efficacy has been demonstrated.

Since the SOLCA Cuenca Cancer Institute is a regional reference in cancer diagnosis and treatment, this study has several strengths. The main limitation is the lack of regional studies that allow reference to the current situation of the problem.

Conclusions

TLSs were found in 5.61% of patients treated at the SOLCA Cancer Institute, Cuenca, from 2010–2020. It is more common in males (57.7%) aged 5 to 11 years. The primary clinical manifestation was dehydration, which was present in 57.7% of patients; however, no deaths associated with TLS were reported. The most common laboratory alteration was hyperuricemia, which was present in 76.9% of patients, followed by hypocalcemia in 73.1%. LDH and GOT levels were also elevated in 88.5% and 69.2%, respectively, of patients. The oncological diagnosis for most patients with TLSs was ALL (61.5%). The basis of treatment was hyperhydration, which was present in all patients, followed by the administration of allopurinol in 80.8% of patients.

Abbreviations

LDH: lactic dehydrogenase.
ALL: acute lymphocytic leukemia.
TLS: tumor lysis syndrome.
ARF: acute renal failure.

Administrative information

Additional Files

None declared by the authors.

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Author contributions

Cárdenas Julissa: Data curation, Formal analysis; Juan Pablo Masías Toapanta: Fund acquisition, Research, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.
Dávila Yasbek: Conceptualization, Data curation, Formal analysis; Juan Pablo Masías Toapanta: Fund acquisition, Research, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.
All the authors read and approved the final version of the manuscript.

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Availability of data and materials

The data are available upon request to the corresponding author. No other materials were reported.

Statements

Ethics committee approval

The study received approval from the University of Cuenca's Health Area Research Bioethics Committee (COBIAS-UCuenca).

Consent for publication

Patient-specific images, MRIs, or CT studies were not available when they were not published.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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