Tumor lysis syndrome in primitive neuroectodermal tumor

Abstract

Tumor lysis syndrome (TLS) consists of a triad of hyperuricemia, hyperphosphatemia, and hyperkalemia along with secondary hypocalcemia. It results from the massive release of intracellular ions from chemosensitive tumor cell death. Hematological malignancies such as acute leukemia and non-Hodgkin lymphoma are considered high risk for developing TLS. Solid tumors are considered less likely to develop TLS. We herein report a case of primitive neuroectodermal tumor developing TLS within 24 h of starting chemotherapy. The child developed severe clinical TLS and could not be saved. We think solid tumors with large tumor load needs to be classified as high risk for development of TLS. Prophylactic use of hyperhydration and other medical measures to prevent TLS is warranted in such cases.

Key words: Pediatric solid tumors, Primitive neuroectodermal tumor, Tumor lysis syndrome, Renal failure, Intrathoracic mass.

INTRODUCTION

The definition of tumor lysis syndrome (TLS) has evolved over the years. The classification proposed by Hande and Garrow (1993) was modified by Cairo and Bishop. Following this classification, laboratory TLS (LTLS) is present if the laboratory value of at least two of the following laboratory parameters are met such as uric acid (8 mg/dl), potassium (6.0 mmol/l), phosphate (2.1 mmol/l), or calcium (below 1.75 mmol/l), or 25% change in the values of above parameters from baseline. Clinical TLS is much rarer and occurs when LTLS is present along with one or more clinical complications such as renal failure (creatinine >1.5 times upper limit of age), cardiac arrhythmias, or seizures. In 2011, Howard et al. revised Cairo and Bishop's definition by adding symptomatic hypocalcemia to be considered diagnostic of TLS. Solid tumors are classified as low risk for the development of TLS. There is a lack of data about the incidence of TLS in pediatric solid tumor. We report a case of a pediatric patient with primitive neuroectodermal tumor developing clinical TLS after initiation of chemotherapy.

CASE REPORT

A 10-year-old boy presented to us with a history of progressively increasing swelling and pain on the right side of the chest for 5 months and cough with difficulty in breathing for 2 months. On examination, the child had severe pallor and bilateral significant (submandibular, jugulodigastric, and axillary) lymphadenopathy. The child had respiratory distress (respiratory rate: 44/min) and required oxygen by mask.
Mediastinal shift to the left side in the form of tracheal shift and shifting of apex beat to 2 cm outside midclavicular line were present. The chest mass on the right side extended horizontally from infrascapular region to the right border of sternum anteriorly (32 cm), vertically from 6th rib in the midaxillary line to below costal margin (18 cm) with hepatomegaly (8 cm below right costal margin). Hemogram and serum biochemistry were within normal limits.

Chest X-ray showed opaque right hemithorax with the shift of the mediastinum to left suggestive of a right-sided mass lesion. The contrast-enhanced computed tomography of chest showed a large heterogeneous mass lesion occupying the entire right thoracic cavity causing complete collapse of the right lung with mediastinal invasion and infiltration of right hemidiaphragm displacing liver to the left hypochondrium in close proximity to vessels with extrathoracic component, bony destruction with speculated perioetal reaction of right 10th rib, suggestive of an aggressive neoplasm likely primary neuroectodermal tumor (PNET) [Figure 1]. Other possibilities kept for aggressive right-sided chest mass were rhabdomyosarcoma and tumors arising from chest wall such as chondrosarcoma and osteosarcomas. Serum lactate dehydrogenase (LDH) was 1853. Fine-needle aspiration cytology of tumor mass was suggestive of malignant small round cell tumor, which narrowed down the possibilities to PNET/Ewing's sarcoma. On day 3 of hospital stay, the child was started on chemotherapy for PNET (ifosfamide and etoposide) after biopsy from the mass. Urine output before starting chemotherapy was adequate (2.8 ml/kg/h). The child developed features of tumor lysis within 24 h of starting chemotherapy. The hemogram and serum biochemistry at baseline and following chemotherapy are shown in Table 1.

![Figure 1: Thoracic extension of the primitive neuroectodermal mass.](image)

The child was started on double hydration (3.0 l/m² potassium free fluid) and allopurinol after he developed an evidence of TLS on day 4. Urea/creatinine values rose from baseline 28/0.6–34/0.7. Phosphate values, serum potassium values, and alanine transaminase/aspartate transaminase values also showed a rising trend. The urine output gradually decreased to 1 ml/kg/h on day 4 of hospital stay and child became anuric in the next 24 h. The child developed shock on the day 6 requiring vasopressor support and mechanical ventilation. The child received broad-spectrum antibiotics. Hemodialysis could not be done due to the persistence of shock. Continuous renal replacement therapy (CRRT) also could not be done due to financial constraints. Chemotherapy was withheld in view of Frank TLS. Acute kidney injury gradually worsened on the anuric fluid regimen. Peritoneal dialysis was started on day 6 of hospital stay with no clinical improvement. We lost the child on day 7 of admission secondary to refractory shock and severe TLS. Biopsy report from the right chest wall mass was suggestive of tumor cells, which were immunopositive for MIC2 and negative for leukocyte common antigen and special stain revealing intracytoplasmic glycogen features suggestive of Ewing sarcoma/PNET.

**DISCUSSION**

In our case, the patient was started on double hydration after biochemical features of TLS developed, but as he developed acute renal failure with hypotension later on, renal replacement therapy in the form of peritoneal dialysis was started. CRRT would have been a better option. CRRT provides hemodynamic stability as well as better uremic clearance and nutritional support to these critically sick patients.[3]

Death of our patient can be also attributed to renal failure due to acute TLS. Bulky tumor mass (>10 cm), high LDH, low urinary flow, and hypotension were the risk factors for the development of TLS in our case. Tumor lysis is far more common in bulky solid tumors than reported earlier (<1%).[4]

The exact incidence of TLS in pediatric solid tumors is not known. Hematological malignancies[6] and various solid tumors with high proliferative rates and responsive to cytotoxic therapy are associated with TLS. For acute leukemia, the incidence of clinical TLS is about 3–7% and 4–11% for lymphomas.[6] However, certain leukemias such as mature B acute lymphoblastic leukemia (ALL)

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**Table 1: Laboratory parameters of the patient**

<table>
<thead>
<tr>
<th>Day</th>
<th>Hb (g/dl)</th>
<th>TLC (l/mm³)</th>
<th>Platelets (l/mm³)</th>
<th>K (mEq/L)</th>
<th>Urea/creatinine (mg/dl)</th>
<th>SGOT/SGPT (U/L)</th>
<th>ALP (U/L)</th>
<th>TSB (mg/dl)</th>
<th>Ca/PO4 (mg/dl)</th>
<th>Uric acid (mg/dl)</th>
<th>TP/Alb (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.8</td>
<td>16,500 N82L18</td>
<td>470,000</td>
<td>4.1</td>
<td>28/0.6</td>
<td>80/15</td>
<td>314</td>
<td>0.5</td>
<td>8.0/3.8</td>
<td>1.1</td>
<td>6.6/3.5</td>
</tr>
<tr>
<td>4</td>
<td>9.0</td>
<td>18,700 N70L30</td>
<td>311,000</td>
<td>5.9</td>
<td>34/0.7</td>
<td>1386/220</td>
<td>-</td>
<td>Not done</td>
<td>8.0/6.3</td>
<td>Not done</td>
<td>7.1/3.7</td>
</tr>
<tr>
<td>5</td>
<td>9.6</td>
<td>17,900</td>
<td>283,000</td>
<td>5.7</td>
<td>75/0.8</td>
<td>1435/410</td>
<td>329</td>
<td>0.8</td>
<td>7.1/10.8</td>
<td>10.8</td>
<td>5.8/2.7</td>
</tr>
<tr>
<td>6</td>
<td>9.6</td>
<td>18,600</td>
<td>216,000</td>
<td>5.8</td>
<td>116/1.2</td>
<td>1340/344</td>
<td>349</td>
<td>0.9</td>
<td>7.0/9.4</td>
<td>10.0</td>
<td>5.4/2.8</td>
</tr>
<tr>
<td>7</td>
<td>8.6</td>
<td>19,200</td>
<td>200,000</td>
<td>5.5</td>
<td>67/0.6</td>
<td>826/441</td>
<td>359</td>
<td>1.1</td>
<td>6.8/4.2</td>
<td>5.3</td>
<td>5.9/2.8</td>
</tr>
</tbody>
</table>

and Burkitt’s lymphoma/leukemia can have high TLS frequency of around 25%.[3]

A number of factors both related to tumor and host associated with an increased risk of TLS in solid tumors are known. The tumor-related risk factors are similar to those associated with the occurrence of TLS in hematological malignancies (ALL) and high-grade non-Hodgkin lymphoma (Burkitt’s lymphoma).[7] However, solid tumors with a high proliferative rate, tumor burden, and sensitivity to cytotoxic therapy can be a potential source of TLS.[1,8]

Around 100 cases of tumor lysis in solid tumors mainly in adults are reported. Literature suggests high mortality rate in solid tumors with tumor lysis.[4] TLS in solid tumors, in contrast to hematological malignancies, occurs after a few days of initiation of chemotherapy.[10] Lesser mortality of TLS in hematological malignancies may be attributed to expectant prophylactic measures while treating them.

Pediatric solid tumors with acute tumor lysis syndrome (ATLS) have been rarely reported in literature. Hain et al. in 1994 has reported only 4 cases of ATLS developing in infants while treating stage IV-S neuroblastoma,[9] while mention has been there in literature of 13 cases of childhood metastatic rhabdomyosarcoma presenting with ATLS and disseminated intravascular coagulation (DIC).[13] The described rhabdomyosarcoma cases had already metastasized to bone marrow causing DIC and behaved similarly like hematologic malignancies with the development of ATLS.

According to evidence-based guidelines of an international expert panel in 2008 for the treatment of TLS, solid tumors are considered low risk (<1%) for developing TLS unless specific host or tumor-related risk factors accompany them. Hence, wait and watch policy is followed in the management of solid tumors in the form of hydration for 24–48 h before starting therapy, and close monitoring for biologic derangements characterizing TLS every 4–6 h for the 1st 48–72 h without any aggressive prophyactic hypouricemic therapy or phosphate binders[8,10] is performed. Established TLS is treated by standard therapy as for hematologic malignancies by aggressive hydration (3–4 L/m²/day) and ensuring diuresis, hypouricemic therapy (allopurinol and rasburicase) along with supportive therapy for metabolic abnormalities.

To summarize, solid tumors with high-risk characteristics as described earlier should be considered to have a high propensity for developing TLS and should be managed in the same lines as acute hematologic malignancies for which modification of guidelines need to be done.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**