



## Spontaneous Fatal Tumor Lysis Syndrome in a Patient with T-Cell Lymphoblastic Lymphoma/Leukemia: Successful Treatment with Continuous Renal Replacement Therapy and Increasing-Dose Gradually Chemotherapy

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### Introduction

Tumor Lysis Syndrome (TLS) results from massive necrosis or apoptosis of large proliferating tumors and is characterized by marked hyperuricemia, hyperkalemia, and hyperphosphatemia secondary to cell lysis and the metabolism of excessive nucleic acids. Clinically significant TLS, with end-organ compromise, occurs in approximately 5% of all patients with hematologic malignancies and in up to 25% of high-risk patients, including those with T-cell acute lymphoblastic leukemia and Burkitt's lymphoma. TLS is a phenomenon frequently occurs after the initiation of therapy, while spontaneous TLS occurring in the absence of chemotherapy, is rare but might portend a worse prognosis. We present a case of spontaneous TLS treated successfully with continuous renal replacement therapy and increasing-dose gradually chemotherapy in a boy with T-cell lymphoblastic lymphoma/leukemia.

### Case Report

A 14-year-old boy presented at the Affiliated Shengjing Hospital, China Medical University, with half a month history of left cervical lymphadenopathy and hemiplegia in right face. There was no fever, night sweats and weight loss. The lymphadenopathy was approximately 3 cm×2 cm in size, discrete, firm and mobile. There were no palpable enlarged lymph nodes in any other region, including the axilla and groin. Full blood count showed white blood cells 7800/μL, hemoglobin 126 g/dL, platelets 290,000/μL. Lymph node biopsy revealed small malignant cells with fine chromatin, convoluted nuclear membranes. On immunohistochemical staining, atypical cells showed positivity for T-cell lineage markers (CD3) and precursor lymphoblastic marker (Terminal deoxynucleotidyl transferase-TdT). Staining for CD20, CD79a and PAX5 was negative. The final pathological diagnosis was precursor T-cell lymphoblastic lymphoma, but he didn't immediately received chemotherapy.

Thirteen days later, he was referred to Liaoning Cancer Hospital. Full blood count showed white blood cells 282,900/μL, hemoglobin 116 g/dL, platelets 67,000/μL, biochemical profile revealed blood urea nitrogen 20.14 (normal 2.5-8.1 mmol/L), creatinine 599.99 (normal 42-133 μmol/L), calcium 1.73 (normal 2.13-2.88 mmol/L), uric acid 2680 (normal 140-420 μmol/L), phosphate 3.89 (normal 0.81-1.65 mmol/L) and potassium 6.0 (normal 3-5.5 mmol/L). He was given treatment with methyl- prednisolone 40 mg per day.

Two days later he was transferred to our hospital with shivering, palpitation and splinter hemorrhage in conjunctiva and skin. Vital signs revealed a blood pressure of 110/70 mmHg, pulse 120/min, respiratory rate of 24/min, temperature 35.6°C. Physical examination showed a painful appearing boy. The abdomen was peaky without palpable mass or splenomegaly. No peripheral lymphadenopathy was palpable. Laboratory data showed white blood cells 277,800/μL,

hemoglobin 81 g/dL, platelets 46,000/μL, blood urea nitrogen 42.83 mmol/L, creatinine 861.0 μmol/L, potassium 8.49 mmol/L, calcium 1.15 mmol/L, phosphate 4.48 mmol/L, bicarbonate 9.0 (normal 19-32 mmol/L), uric acid 3880 μmol/L, lactate dehydrogenase 3068.0 (normal 109-245 U/L), aspartate transaminase 95 (normal 8-50 U/L), glutamyl transpeptidase 132 (normal 8-78 U/L) and alkaline phosphatase 150 (normal 38-126 U/L). ECG revealed high and sharp T wave.

Under the impression of spontaneous fatal tumor lysis syndrome, the patient was given immediately sodium bicarbonate in order to improve acidosis, forced diuresis with furosemide, calcium gluconate, glucose and insulin infusion for hyperkalemia, further hydration and allopurinol for hyperuricemia, and continuous renal replacement therapy (CCRT) was administered 4 hours on admission, which lasted 8 hours. Then dexamethasone 10 mg was administered for low-dose chemotherapy. The data showed blood urea nitrogen 38.03 mmol/L, creatinine 531.0 μmol/L, potassium 6.32 mmol/L, calcium 1.08 mmol/L, phosphate 4.28 mmol/L, bicarbonate 17 mmol/L, uric acid 3480 μmol/L, white blood cells 52,500/μL, hemoglobin 75 g/dL, platelets 47,000/μL after 10 hours' treatment. Then the patient was continued the above treatment except CCRT. The data showed blood urea nitrogen 45.4 mmol/L, creatinine 650.0 μmol/L, potassium 6.27 mmol/L, calcium 1.10 mmol/L, phosphate 3.89 mmol/L, bicarbonate 17 mmol/L, uric acid 3477 μmol/L, white blood cells 12,400/μL, hemoglobin 67 g/dL, platelets 27,000/μL after 34 hours' treatment. The laboratory parameters of this patient are summarized in Figure 1A and 1B.

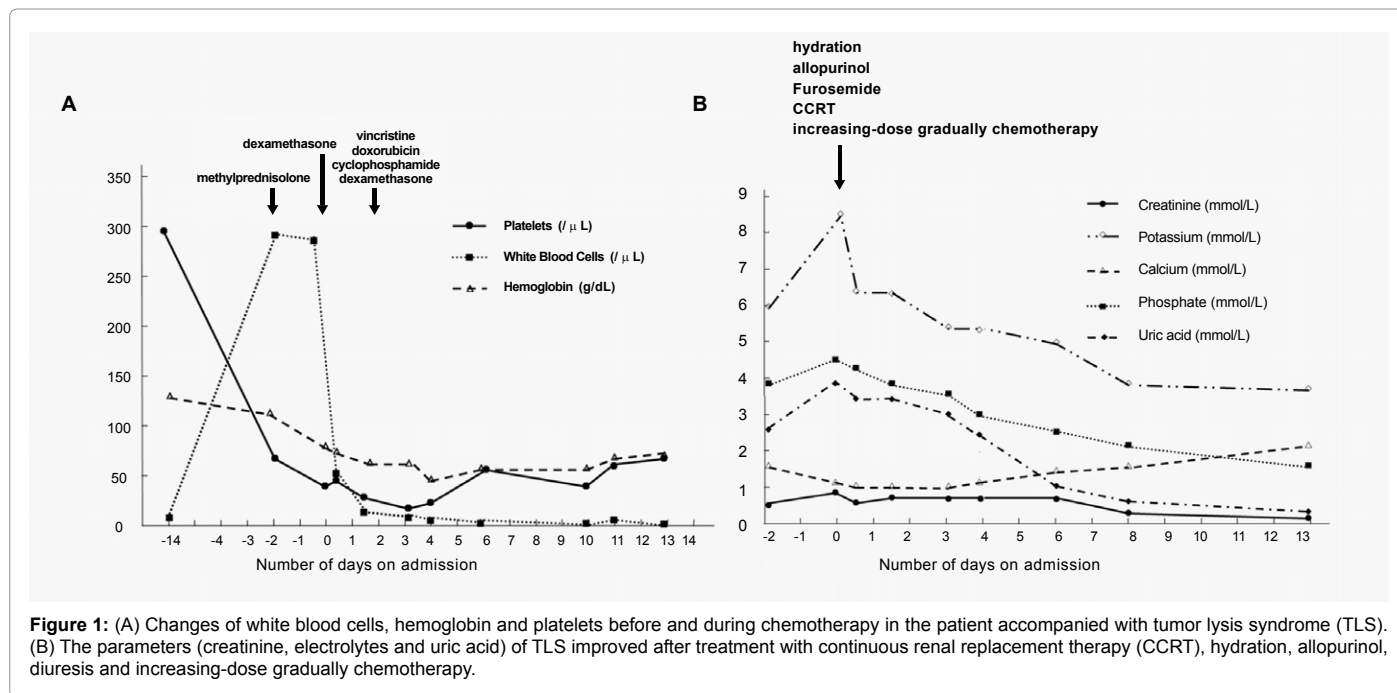
For staging, bone marrow aspiration/biopsy and diagnostic spinal tapping (for Cerebrospinal Fluid Cytology CSF) were performed. Bone marrow aspiration/biopsy revealed lymphocytic infiltration without preservation of other cell lines. On cytochemical staining lymphocytes showed positivity for Nonspecific Esterase (NAE) and periodic acid Schiff (PAS) and negativity for myeloperoxidase (POX). And flow cytometry detected CD2, CD5, CD7, cCD3 and TdT was positive. There was no evidence of lymphoma involvement in CSF. Based on the above findings, the diagnosis of T-cell lymphoblastic lymphoma/leukemia and tumor lysis syndrome was made.

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The patient subsequently underwent increasing-dose gradually chemotherapy (vincristine 1.0 mg/m<sup>2</sup> day 1 and 1.4 mg/m<sup>2</sup> days 8,15,22; doxorubicin 40 mg/m<sup>2</sup> days 1,2,15,16; cyclophosphamide 650 mg/m<sup>2</sup> day 1 and 750 mg/m<sup>2</sup> day 15; dexamethasone 10 mg/m<sup>2</sup>×28) on the second day of admission. Duration of the chemotherapy, the patient was given further hydration, forced diuresis with furosemide to maintain urinary output >200 ml/h, and allopurinol to reduce uric acid. CCRT was administrated again for 4 hours on the second day of chemotherapy in order to prevent the relapse of TLS, at the same time, white blood cells dropped to 6100/μL. Hyperkalemia was relieved on the third day of admission, hyperuricemia and renal insufficiency were relieved on the thirteenth day of admission, and bone marrow smear revealed complete response on the twenty-fifth day of admission.

## Discussion

Tumour lysis syndrome is well established in association with hematologic malignant diseases, specifically acute leukemia and non-Hodgkin lymphoma [1]. Spontaneous TLS, referring to manifestations of TLS in patients who have not received cytotoxic therapy, is very rarely described in the medical literature. Froilan Torres C had ever collected only 22 documented cases (Medline 1960-2008, key words: tumor lysis syndrome, spontaneous) [2]. On this basis, we collected again 7 documented cases [3-9], (Medline 2009-2013). Overall, summarized as follows: 7 of these cases were associated with leukemia (2 lymphoblastic leukemia) [10,11], 2 were linked to germinal cells, 1 were linked to Crohn's disease, 9 were linked to solid tumors, and 10 to lymphoma. Here, our patient was a boy with T-cell lymphoblastic lymphoma/leukemia complicated spontaneous fatal acute tumor lysis syndrome.

Most guidelines indicate that the risk of tumor lysis syndrome is based on two factors. First, the risk is related to the malignancy itself. Increased size of the cancer mass and involvement of other organs and bone marrow increase the risk. The cell lysis potential of the cancer, including the proliferative ability and chemosensitivity of the tumor, also poses a risk for tumor lysis. Second, patient factors such

as dehydration and renal failure make the clearance of intracellular metabolites more difficult, thus increasing the risk of tumour lysis. The risk factors for developing acute TLS in patients with lymphoblastic lymphoma/leukemia are male sex, age ≥ 10 years, splenomegaly, mediastinal mass, central nervous system involvement, lactate dehydrogenase ≥ 2000U/L, and white blood count ≥ 20/μL [12,13]. Our patient was a boy, 14 years old, lactate dehydrogenase 3068 U/L, white blood count 282.9/μL, and bone marrow involvement, So the patient developed a fatal acute tumor lysis syndrome.

The treatment of spontaneous TLS is same to TLS secondary to chemotherapy. Hydration, preferred method of increasing urine output, can rapidly improve renal perfusion and glomerular filtration and minimize acidosis and oliguria. Our patient was infused 2500 ml per square meter per day fluids. Allopurinol and rasburicase can preserve or improve renal function and reduce serum phosphorus levels as a secondary beneficial effect by reducing the level of uric acid, and rasburicase is more effective than allopurinol for the prevention and treatment of the tumor lysis syndrome by preventing xanthine accumulation and directly breaking down uric acid. At the time of the study, rasburicase was not available in China, so allopurinol was administered. Urinary alkalinization, which could increase uric acid solubility but decrease calcium phosphate solubility, should be discontinued when hyperphosphatemia develops. Our patient was immediately given sodium bicarbonate on admission in order to improve acidosis, but sodium bicarbonate was stopped as soon as the acidosis was rectified, because of the existence of hyperphosphatemia. Hypocalcemia is secondary to hyperphosphatemia. Symptomatic hypocalcemia should be treated with calcium at the lowest dose required to relieve symptoms, since the administration of excessive calcium increases the calcium-phosphate product and the rate of calcium phosphate crystallization. Our patient accompanied with hyperkalemia, so calcium gluconate was used to reduce the risk of dysrhythmia while awaiting hemodialysis, at the same time glucose plus insulin was also given to urge potassium afflux into intracellular. Although the incidence of patients requiring hemodialysis has

decreased, up to 5% of all patients diagnosed with TLS still need the procedure. Because of hyperkalemia and hyperphosphatemia, so continuous renal replacement therapy was administered 4 hours on admission, which lasted 8 hours.

Considering patients at high risk for the tumor lysis syndrome may also receive low-intensity initial therapy [14]. Slower lysis of the cancer cells allows renal homeostatic mechanisms to clear metabolites before they accumulate and cause organ damage. This strategy, in cases of advanced B-cell non-Hodgkin's lymphoma or Burkitt's leukemia, has involved treatment with low-dose cyclophosphamide, vincristine, and prednisone for a week before the start of intensive chemotherapy [15]. On the basis of above mentioned therapy, the patient was given dexamethasone 10mg for low-dose chemotherapy day 0 and 1 on admission, subsequently underwent incremental gradually chemotherapy when white blood cells was no more than 20,000/ $\mu$ L, simultaneously TLS was continued to be prevented recurrence. Then hyperkalemia was relieved on the third day of admission, hyperuricemia and renal insufficiency were relieved on the thirteenth day of admission, and bone marrow smear revealed complete response on the twenty-fifth day of admission.

The etiology of the spontaneous TLS is unclear at this point. There are various hypotheses including increased production of glucocorticoids and hyperthermia which lead to increased tumor cell death [7]. Hyperphosphatemia is less common in spontaneous than nonspontaneous TLS, possibly because phosphate release in lysis is less achievable when cytotoxic therapy has taken place. More research needs to be done in order to better understand caused of spontaneous TLS and prevent its occurrence.

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