CASE REPORT: SPONTANEOUS TUMOR LYSIS SYNDROME IN HEMATOLOGICAL MALIGNANCY

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INTRODUCTION

Acute tumor lysis syndrome (TLS) is multiple metabolic derangements that occur due to the treatment of malignancies or spontaneous tumor cells death. By the destruction of tumor cells; a large amount of uric acid, potassium, phosphate and purine metabolites; circulate in the blood. During TLS hyperuricemia, hyperkalemia,hyperphosphatemia develops and ,as a result of the collapse of calcium phosphate crystals, hypocalcemia occurs. Acute renal failure occurs due to the precipitation of calcium phosphate and uric acid. TLS, as a result of acute renal failure and multi–organ failure, leads to high morbidity and mortality. (1)

Non-Hodgkin's lymphoma, Burkitt's lymphoma, other aggressive B-cell lymphomas, acute lymphoblastic lymphoma and other hematological malignancies are associated with higher risk of the occurrence of the acute TLS .(7,8) It can also occur in solid cancers. Spontaneous TLS is a very rare occurrence, which has also been described with both hematological and solid malignancies. (9, 10) TLS is often seen at the first 5 days of treatment or after surgery and embolization. TLS may occur spontaneously with high proliferative tumors. (1) Spontaneous TLS is rare but there remains the possibility of worse clinical outcomes because of the lack of benefit of pre-treatment. (4). Risk factors for developing acute TLS after initiation of chemotherapy in all tumors are uric acid level > 7.5mg/dL at initiation of treatment, underlying renal insufficiency, creatinine > 1.6mg/dL, hypercalcemia, leukocytosis > 50,000m^3, bulky disease, high LDH, high tumor growth fraction. (5, 6)

The etiology of the spontaneous TLS is unclear. Fortunately spontaneous TLS is rare but there remains the possibility of worse clinical outcomes due to lack of benefit of pre-treatment. Also, because these patients are often not under the care of oncologists, the syndrome may go unrecognized, which delays appropriate treatment. Therefore, it is imperative that general clinicians are able to recognize the syndrome and initiate adequate care. (4)

The prediction of the cases is the ideal therapeutic approach to minimize the morbidity and mortality for TLS. In all newly diagnosed malignancies plasma urea, creatinine, sodium, potassium, calcium-phosphate, magnesium and uric acid levels to should be determined. The most important aspects for treatment of TLS are hydration and treatment of hyperuricemia. (3)

We present a case of spontaneous TLS in a male with a late diagnosis of T-cell leukemia/lymphoma.

CASE

71 year old male patient referred to our hematology department from another center with elevated blood cell levels in May 2012 had values; white blood cells (WBC) 44000, hemoglobin (HB) 15.5 g/dl and platelet count 158000. Patient didn't have any findings in his physical examination and no pathologic scale lymphadenopathy (LAP) or organomegalia was detected in his cervical, thoracic and abdominal CT. His bone narrow aspiration was pre-diagnosed as lymphoproliferative disorder, chronic lymphocytic leukemia (CLL) and large granular lymphocytic leukemia (LGL). In his bone marrow biopsy 50% cellularity and up to 15-20% lymphoid populations among all cells were observed. Though presenting small lymphoid morphology, in immunohystochemical examinations presents CD3(+), CD5 patched (+), CD8 in rare cells (+), CD4(-), CD20(-), cyclin D1(-), CD10(-), CD23(-), bcl-2(-) immunophenotype. Although these cell values are in favor of a T-cell lymphoproliferative disorder, they are not adequate for a precise diagnosis. Patient was advised to be reevaluated by a re-biopsy after a appropriate time period. Afterwards, patient who didn't show up in the follow-ups referred to our clinic with complaints such as nausea, fatigue and lack of appetite in July 2012. After detection of cervical, inguinal and axillary pathologic lymphadenopathy and hepatosplenomegaly ;patient's bone marrow aspiration and biopsy examinations are repeated. In immunophenotyping values are measured as CD2 99.7%, CD3 89.8%, CD4 98.5%, CD5 41.6%, CD8 2.1%, CD22 6.4%, CD20 0.1%, CD23 2.5%, CD33 54.5%, CD34 0.6%, CD45 97.8%, CD10 0%, CD13 6.2%, CD14 0.1%, CD19 0.4%, CD7 22.3%, TdT 0%, HLA-DR 10.3%, CD25 51%, CD1a 0%, CD16+56 46.3%. LAP excision is made from right axillary area. Before receiving bone marrow biopsy and LAP excision pathology reports patient referred to emergency service due to oliguria, respiratory distress, high fever and general condition failure. Patient was admitted to internal medicine intensive care unit pre-diagnosed with lymphoproliferative disorder, acute renal failure and sepsis. In physical examinations general condition was bad, heart rate (HR) was 115/min, blood pressure (BP) was 90/60 mmHg, respiration rate (RR) was 25/min and body temperature (BT) was 37.8^{o}C. 1.5 – 2 cm wide LAPs in cervical and left axillary areas and 2 cm wide LAPs in both inguinal areas were detected. Liver was palpable up to 5cm below arcus costae and Traube's space was dull. There were fine crackles (rales) bilaterally in both lung bases. Laboratory measurements were as follows: Hb: 13.7gr/dl, WBC: 119,800/mm^3, HTC: 41.9%, PLT: 101.000/mm3, ESR: 38 mm/h, CRP: >204, PT: 14.6sec, INR: 1.25, APTT: 27.9sec, Urea: 149 mg/dl, Creatinine: 3.70 mg/dl, Uric Acid: 11.1 mg/dl, AST:156 U/Lt, ALT: 38 U/Lt, T. Biluribin: 4.00, LDH: 1525, T. Protein: 6.1 gr/dl, Albumin: 2.0 gr/dl, K:6.1 mmol/Lt, P: 7.0 mg/dl, Mg: 2,9 mg7dl, Na: 146 mmol/Lt, Corrected Calcium: 9.3 mg/dl, Ferritine: 937.4, Vit. B: 289, Folic Acid: 5.84, pH: 7.43, HCO_3: 18.9 mmol/Lt, PaO_2: 72.2 mm/Hg, $PaCO_2$: 37.8 mm/Hg.

Patient was diagnosed as rapidly progressive lymphoproliferative disorder and spontaneous tumor lysis and intravenous hydration was initiated. Due to patient's anuric condition patient was hydrated under control. Patient was treated with inotropes due to hypotension. Buffered

fluid treatment was initiated for patient's hyperkalemia while he didn't any specific ECG findings. Also oxygen support was provided to avoid hypoxia. Due to his high fever and hypotension appropriate antibiothreapy applied to the patient since he admitted to ER in septic shock state. Urgent dialysis was performed due to anuria, progressive elevation of potassium values and development of metabolic acidosis (pH: 7.04, HCO_3: 9.9mmol/Lt, PaO_2: 86.5 mm/Hg, $PaCO_2$: 37.8mm/Hg). To avoid hypotension dialysis was performed under inotrope support. While respiration distress and tachypnea was becoming more evident in patient, cardiac echography detected no findings in the favor of pulmonary embolism. Left and right cardiac functions were normal. Since pulmonary screenings and examination findings made a lower respiratory tract infection less probable and there was no reason to explain acute renal failure patient was diagnosed as spontaneous tumor lysis syndrome and multiple organ dysfunction syndrome. During observation patient lost his consciousness, there was no recovery in his metabolic status and his hypotension worsened. Due to this conditions patient developed cardiopulmonary arrest and didn't answer CPR and passed away.

Pathology reports from bone marrow biopsy dated July 31st 2012 was collected after the death of patient. Biopsy was reported as NK/T-cell leukemia. Cellularity was 70% and 50% of all the cells were neoplastic lymphocytes. Immunohistochemical examinations presents neoplastic lymphoid cells CD3(+), CD20(-),CD2(+),CD5(-),CD4(-),CD8(-),CD57(-),CD56(-),CD16(+),granzyme (+/-),TdT(-), cyclin D1(-), CD23(-), CD30(-), CD10(-). When it was evaluated along with patient's lymph node sample most probable diagnosises were mature T cell leukemia / lymphoma and aggressive peripheric NK cell leukemia. Less probable diagnosises could be extranodal NK/T cell lymphoma, peripheric T cell lymphoma and NOS's rare observed immunophenotyped variants.

Consistent with bone marrow biopsy, July 31st 2012 dated right axillary LAP excision was reported as NK/T cell leukemia. Within lymph node, a structure destructing ,diffuse neoplastic infiltration which was more likely consisted of medium and large lymphoid cells was observed. Immunohistochemical examinations were as follows: CD3(+), CD20(-), CD2(+), CD5(-), CD4(+), CD7(-), CD8(-), CD57(-), CD56(+), CD16(+), granzyme(+/-), ALK(-), CD30(+), CD43(+), TdT(-), cyclin D1(-), CD23(-), CD30(+), CD10(-), EBV LMP1(-), Ki67 proliferation index %100. Primary diagnosis was mature T cell leukemia / lymphoma, aggressive NK cell leukemia.

DISCUSSION

Acute tumor lysis syndrome is a catastrophic condition of multiple metabolic derangements that occur due to the rapid destruction of tumor cells with massive release of cellular breakdown products, typically seen following the treatment of malignancies. The syndrome is characterized by the rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, metabolic acidosis and acute renal failure. (11) When the syndrome is seen prior to the institution of therapy, it is termed spontaneous tumor lysis syndrome. Acute spontaneous tumor lysis syndrome has been usually described in association with hematologic malignancies such as leukemia and lymphoma. Rare reports of acute spontaneous tumor lysis syndrome in solid tumor malignancies involved gastrointestinal adenocarcinoma, germ cell tumors, gastric carcinoma, inflammatory breast carcinoma, colon carcinoma, malignant

pheochromocytoma, hepatocellular carcinoma, prostate cancer, and adenocarcinoma of the lung. (12)

Acute spontaneous tumor lysis in aggressive T-cell lymphoma, as our case, was reported in 2 cases in the literature before. First case; acute spontaneous tumor lysis in anaplastic large T-cell lymphoma presenting with acute renal failure was reported in 2004 from Chang Gung Memorial Hospital, Taiwan. The second case was spontaneous tumor lysis syndrome presenting with pancytopenia and acute renal failure in peripheral T cell lymphoma reported in 2011 from Chosun University Hospital, Republic of Korea.

The exact mechanism of spontaneous TLS is still uncertain. Release of intracellular metabolites due to rapid tumor necrosis was suggested to play a role for development of spontaneous acute TLS. Acute TLS is one of the most significant causes of acute renal failure (ARF) among malignancy patients. ARF that results from acute TLS is usually oligoanuric and has multifactorial etiology. Acute renal failure in our case was also oligoanuric form. The most important cause of ARF is precipitation of uric acid in the tubules of kidney due to hyperuricemia caused by increased turn-over of nucleic acids. Hyperphoshatemia contributes to renal failure by deposition of calcium phosphate complex in the renal interstitium. (13)

The potential causes of spontaneous TLS are unknown. The case report literature presents two theoretical causes of spontaneous TLS including endogenous secretion of glucocorticoids and hyperthermia. Although more commonly described in lymphoid malignancies, exogenous corticosteroid-induced TLS has not been demonstrated in AML and was reported only once in MDS. (14)

The staple of TLS treatment is prevention. Unfortunately, this is unavailable when presented with a case of spontaneous TLS. The first step in managing hyperuricemia is adequate hydration. Patients should receive 2 to 4 times the daily fluid maintenance unless there are contraindications to large fluid volumes from other co-morbidities. The increased urine output should help with excretions of uric acid and phosphate. The general consensus is that the urine output should be above 100 mL/m2/h. If the urine output is still inadequate despite hydration, diuretics should be used (loop diuretics such as furosemide are first-line; osmotic agents such as mannitol have also been utilized. Recent expert guidelines have recommended against alkalinization of urine due to inadequate data on benefits and potential complications from the therapy. A recent addition to the armamentarium for treatment of hyperuricemia in TLS is recombinant urate oxidase/rasburicase. Urate oxidase is effective for prevention of TLS in high-risk patients prior to initiation of therapy. Allopurinol can also be used, but it has major limitations. First, it only blocks the production of new uric acid without any effect on uric acid already in circulation. It can also cause xanthine nephropathy. In addition, because it is renally cleared, clinicians must use allopurinol carefully in those with impaired renal function.(4)

Patient’s electrolytes and renal functions have to be monitored closely. Although the incidence of patients requiring dialysis has decreased down to 5% of all patients diagnosed with TLS still need the procedure. (4) Due to anuria, metabolic acidosis and hyperkalemia our patient has been in need of dialysis in our case.

More research needs to be done in order to better understand causes of spontaneous TLS. Fortunately, spontaneous TLS is rare but there remains the possibility of worse clinical outcomes because of the lack of benefit of pre-treatment. Also, because these patients are

often not under the care, the syndrome may go unrecognized, which delays appropriate treatment. Therefore it is imperative that general clinicians are able to recognize the syndrome and initiate adequate care.(4)

REFERENCES

1-Fox K. Oncologic emergencies. In: Macdonald J, HallerD, Mayer R, eds. Manual of oncologic therapeutics.Philadelphia: Lippincott, 1995:347-77

2-Malcolm L.Bridgen MD. Hematologic and Oncologic Emergencies; Doing the most good in the least time. Postgraduate Medicine Vol 109 (3) 2001

3-Schilsky RL. Renal and metabolic toxicities of cancer chemotherapy.Semin Oncol 1982;9(1):75-83

4-Mateusz Opyrchal, Travis Figanbaum, Amit Ghosh, Vincent Rajkumar, and Sean Caples. Spontaneous Tumor Lysis Syndrome in the Setting ofB-Cell Lymphoma. Case Reports in MedicineVolume 2010, Article ID 610969, 3 pages doi:10.1155/2010/610969

5-E. Rampello, T. Fricia, and M. Malaguarnera, "The management of tumor lysis syndrome," *Nature Clinical Practice Oncology*, vol. 3, no. 8, pp. 438–447, 2006.

6- A. Tufan, N. Unal, E. Koca, I. Onal, S. Aksu, and I. Haznedaroglu, "Spontaneous tumor lysis syndrome in a patient with diffuse large B cell lymphoma and Richter syndrome," *Annals of Hematology*, vol. 85, no. 3, pp. 183–184, 2006.

7- K. R.Hande and G. C. Garrow, "Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma," *American Journal of Medicine*, vol. 94, no. 2, pp. 133–139, 1993.

8- W.Wossmann, M. Schrappe, U.Meyer,M. Zimmermann, and A. Reiter, "Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase," *Annals of Hematology*, vol. 82, no. 3, pp. 160–165, 2003.

9-C. Gemici, "Tumour lysis syndrome in solid tumours," *Clinical Oncology*, vol. 18, no. 10, pp. 773–780, 2006

10- M. Lotfi and J. M. Brandwein, "Spontaneous acute tumor lysis syndrome in acutemyeloid leukemia? A single case report with discussion of the literature," *Leukemia and Lymphoma*, vol. 29, no. 5-6, pp. 625–628, 1998.

11-. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004; 127:3–11.

12-Acute spontaneous tumor lysis syndrome in a patient with squamous cell carcinoma of the lung. Q J Med 2009; 102:71–73

13- AYLA GOKMEN AKOZ , NESLIGUL YILDIRIM , HUSEYIN ENGIN , SIMTEN DAGDAS , GULSUM OZET , ISHAK OZEL TEKIN , FUNDA CERAN. An unusual case of spontaneous acute tumor lysis syndrome associated with acute lymphoblastic leukemia: A case report and
review of the literature. Acta Oncologica, 2007; 46: 1190_1192

14- Brett Riccio Anthony Mato ,Erin M. Olson Jeffrey S. Berns .Selina Luger .Spontaneous Tumor Lysis Syndrome in Acute Myeloid Leukemia [Cancer Biology & Therapy 5:12, 1614-1617, December 2006];