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CASE REPORT

Treatment of tumor lysis syndrome with the highest known uric acid level

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ABSTRACT

Tumor lysis syndrome (TLS) is a disease with high mortality that develops in conditions characterized by rapid cell proliferation or after the cytotoxic treatment of malignant diseases. Extraction of intracellular ions and metabolites into the extracellular milieu following cell destruction causes hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and uremia. The prophylaxis and treatment of TLS includes intensive hydration, diuretics, alkalinization of the urine, allopurinol, and rasburicase. Close electrolyte monitoring of the patients is required. In the patients with acute renal failure (ARF), dialysis can be used either as the first treatment of choice or together with the above-mentioned prophylactic and therapeutic agents. Herein we report the effective treatment of a patient with anuric ARF by means of sequential hemodialysis sessions, in whom TLS developed after chemotherapy; the uric acid level was 71.3 mg/dL, which was considerably greater than the values reported in the literature.

Keywords: tumor lysis syndrome; hemodialysis; hyperuricemia; acute renal failure

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INTRODUCTION

Tumor lysis syndrome (TLS) is a disease that develops in conditions characterized by rapid cell proliferation and/or after the cytotoxic chemotherapy. TLS results from the extraction of intracellular ions, nucleic acid, protein, and other metabolites into the extracellular milieu due to the destruction of malignant cells. TLS is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and uremia.[1,2] Mortality due to TLS in hematologic malignancies is approximately 36%.[3] The primary mechanism underlying the development of acute renal failure (ARF) in patients with TLS is the increase in uric acid excretion and obstruction of the renal tubules caused by uric acid crystals due to decreased solubility, particularly in acidic urine. Another mechanism involves calcinosis due to the high phosphate level and deposition of calcium–phosphate crystals in the renal interstitium and tubular system.[4]

To prevent TLS, it is essential to initiate prophylaxis, particularly in patients with a high tumor burden or in those with renal damage at the onset of treatment. The primary goal of prophylaxis is to achieve a decrease in the uric acid level; a second goal of prophylaxis is to increase excretion. Intensive hydration, urinary alkalinization, allopurinol, rasburicase, and dialysis are treatment options that can be used in prophylaxis and/or treatment.[1]

Herein, we report effective treatment of a patient with anuric ARF by means of sequential hemodialysis sessions, in whom TLS developed after chemotherapy and the uric acid level (71.3 mg/dL) was considerably greater than the highest value reported in the literature.

CASE

A 19-year-old male patient, who had been followed and treated in the Hematology Department for approximately 1 year with the diagnosis of T-cell acute lymphoblastic leukemia (T-ALL), admitted to our hospital with complaints of weakness, fever, abdominal pain, diffuse rash over his body, and difficulty with urination for 1 day. Cyclophosphamide (1 g/day) and prednisolone (64 mg/day) had been administered 2 days before his complaints began. At the time of admission, his general status was moderate-poor, there were

diffuse petechial lesions over his body, his mucosa and conjunctivae were pale, and his spleen was palpable 2 cm below the costal margin. The patient was considered to have relapsed ALL and TLS and was thus hospitalized.

The patient was anuric and had uremic encephalopathy for 1 day at the time of admission. He was considered to have ARF due to tumor lysis as he had hyperkalemia, hyperuricemia, hyperphosphatemia, and elevated creatine kinase and lactate dehydrogenase (LDH) levels on biochemical analysis. Because the patient was anuric and euvolemic, his total fluid intake was restricted to 1500 cc. Neither diuretic therapy nor urinary alkalinization was administered because the patient had no urinary output. Because of impaired renal function, allopurinol treatment was not initiated. As he had uremic symptoms and electrolyte imbalance, hemodialysis therapy was initiated. A 3-hour hemodialysis was performed with a 1.3 m^2 synthetic membrane, with a blood flow rate of 150 mL/min and a dialysate flow rate of 500 mL/min. As he had no urinary output and the hyperuricemia persisted, the patient underwent a 6-hour hemodialysis after 8 hours with a 1.3 m^2 synthetic membrane at a blood flow rate of 150 mL/min and a dialysate flow rate of 500 mL/min, though the encephalopathic entity and hyperkalemia improved. The biochemical parameters in the middle and at the end of the second hemodialysis session are presented in Table 1. Urinary output began (300 cc/day) the following day; however, he underwent a third dialysis session (a 5-hour hemodialysis with a 1.6 m^2 synthetic membrane, a blood flow rate of 250 mL/min, and a dialysate rate of 500 mL/min) because he was oliguric and his hyperuricemia persisted. On the third day of hospitalization, the urinary output was 2 L/day. Polyuria appeared on the fourth day with a urine output of 4 L/day. His body weight was monitored daily and he was hydrated taking into consideration insensible losses as well as urine output. Polyuria persisted for 12 days, with a maximum daily urinary output of 12 L. On the 13th day of follow-up, the creatinine level had decreased to 1.7 mg/dL, and allopurinol therapy was initiated at a dose of 300 mg/day. On the 17th day of follow-up, the renal function had completely improved and he was discharged with a daily urinary output of 2.5 L.

TABLE 1. Biochemical parameters of the patient.

	At the time of admission	First day after the first dialysis	First day at the middle of the second dialysis	After the second dialysis	Second day after the third dialysis	Seventeenth day
BUN (mg/dL)	69	43	63	25	27	24
Cr (mg/dL)	3.6	1.9	3.5	1.6	3.2	0.8
TP (g/dL)	5.5					6.4
Alb (g/dL)	3					3.9
AST (U/L)	1911		967	819	208	19
ALT (U/L)	78		226	274	154	15
Ca (mg/dL)	7.4		7	8.9	8.1	8.7
P (mg/dL)	12.7		10.9	4.7	4.4	2.2
LDH (U/L)	27,980				7,648	2,773
CK (U/L)	1032			497	162	
Na (mmol/L)	133	140	135	138	132	145
K (mmol/L)	8.9	3.7	4	3.7	3.7	3.8
UA (mg/dL)	71.3	31.3	36.1	11.2	11.5	4.2
WBC (μL)	182,000	153,000	18,800	7,500	1,900	2,100
Hb (g/dL)	7.8					8.1
HCT (%)	22.9					24
PLT (μL)	24,000		18,000	18,000	32,000	72,000

Notes: BUN, blood urea nitrogen; Cr, creatinine; TP, total protein; Alb, Albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ca, calcium; P, phosphorus; LDH, lactate dehydrogenase; CK, creatine kinase; Na, sodium; K, potassium; UA, uric acid; WBC, white blood cells; Hb, hemoglobin; HCT, hematocrit; PLT, platelets.

DISCUSSION

TLS is a potentially fatal metabolic complication that spontaneously occurs in rapidly proliferating drug-sensitive tumors or rarely occurs after treatment.[4] TLS generally begins 12–72 hours after cytotoxic therapy.[1] The diagnosis of TLS is made clinically. The syndrome results from the death of rapidly proliferating tumor cells and the extraction of intracellular purines, phosphate, and potassium into the extracellular milieu.[5,6] An elevated LDH level is associated with tumor size.[7] The patient described herein had received chemotherapy 2 days before his admission to the hospital, had a high tumor burden, and had the white blood cell count of 182,000 μL. Correlating with the amount of tumor burden, the LDH level was 27,980 U/L. On follow-up visits, the LDH level decreased to 2773 U/L.

TLS, which is one of the causes of ARF, is frequently encountered in malignancies. TLS is more frequently observed in patients with volume depletion or preexisting renal damage. The fluid intake of the presented patient was not sufficient due to nausea and vomiting caused by the chemotherapy, thus ARF occurred as he also had a high tumor burden. TLS is usually reversible; however, it is accompanied by severe metabolic disorders. The primary mechanism leading to ARF in TLS is uric acid elevation. Uric acid, which results from nucleic acids that are released due to the destruction of rapidly proliferating cells, is deposited in the collecting tubules, as well as in the deep cortical and medullary tubules.[7,8] After uric acid is deposited in the tubules, it leads to local granulomatous inflammation in addition to obstruction. Furthermore, uric acid may cause ARF through renal vasoconstriction by reduction of the synthesis of endothelial nitric oxide, inhibition of the proliferation and migration of endothelial cells, activation of apoptosis, activation of the release of proinflammatory cytokines, increment of the free oxygen radicals, and impairment in renal autoregulation.[9] TLS frequently causes oligoanuric renal failure. The other electrolyte disorder in TLS syndrome is the elevation of phosphorus. High phosphorus levels form calcium–phosphate complexes and deposits in the renal interstitium and tubular system, thus causing ARF.[7,8]

The uric acid level of the presented patient became abnormally high in a short time after chemotherapy. A possible genetic defect that may lead to such an elevation was not considered as the uric acid level before chemotherapy was normal and such an elevation had not been observed during previous therapies. Moreover, the patient did not receive any medications except for chemotherapy that would increase the level of uric acid. He did not have gout. The uric acid elevation in the patient was considered to be related to the high tumor burden and the lack of sufficient hydration that would remove the metabolites resulting from excessive cell destruction after the chemotherapy.

The approach to TLS should primarily focus on a detailed medical history and physical examination, as such in all patients with ARF. The order of the treatment options including hydration, urinary alkalinization, allopurinol, rasburicase, diuretics, and dialysis varies according to the volume status of the patient, as well as the urinary output.

In patients without hypervolemia, renal influence due to elevated uric acid is reduced via intensive intravenous (IV) hydration.[7] Intensive IV hydration is accepted as 3 L/m^2/day. The intravascular volume, renal blood flow, glomerular filtration, and excretion of uric acid, and phosphorus is increased by hydration. After obstructive uropathy is eliminated and sufficient IV hydration is achieved in hypovolemic patients, diuretic therapy is also recommended in the treatment of TLS to keep the urinary output above 100 mL/m^2/hour. Mannitol (0.5 mg/kg) and furosemide (2–4 mg/kg) are the recommended diuretics.[1] Because the presented patient was anuric and did not have hypervolemia, diuretics were not administered.

In patients with urinary output and without pulmonary edema, alkalization of urine is recommended for the prevention and treatment of TLS. Urinary alkalization to a urinary pH ≥ 6.5 can be achieved using sodium bicarbonate. The solubility of uric acid increases in alkali urine, and the deposition of uric acid crystals is prevented. However, the solubility of xanthine and hypoxanthine decreases at the urinary pH ≥ 7. When alkali therapy is administered together with allopurinol, formation of xanthine crystals increases.[10]

One of the main goals in the treatment of TLS is to decrease the uric acid level. The uric acid level can be lowered by preventing uric acid formation either with allopurinol, which is a xanthine oxidase inhibitor, or with rasburicase, which is a recombinant urate oxidase. Although hydration, urinary alkalization, and allopurinol are administered for prophylaxis, ARF may develop by 14–25%, particularly in high-risk patients. In recent years, it has been demonstrated that the uric acid level is effectively kept under control with the use of rasburicase. However, there are limited number of clinical studies regarding its creatinine-lowering effect and its effect on the need for dialysis.[10,11]

A need for dialysis may be observed despite IV hydration, urinary alkalization, and the use of allopurinol in patients who have extensive hydration and urinary output. The metabolic complications of ARF, hyperkalemia, volume overload, uremia, uric acid, and phosphorus elevation, are effectively treated with hemodialysis. The plasma uric acid level can be reduced

by 50% with a 6-hour hemodialysis session.[7] The phosphorus level is also effectively reduced with hemodialysis. Rebound in uric acid and phosphorus levels is substantially low. Uric acid and phosphorus can return to normal values with approximately two or three hemodialysis sessions.[4]

In the presented patient we performed hemodialysis as the first treatment of choice because the patient had anuria, renal function impairment, uremic symptoms such as nausea and vomiting, and electrolyte imbalance during the initial evaluation. After a 3-hour hemodialysis performed with a 1.3 m^2 synthetic membrane, a decrease by 55% was achieved in the uric acid level. After a second hemodialysis session for 6 hours, a decrease in uric acid level by 84% and in phosphorus level by 62% was achieved compared to the baseline. Our higher results, as compared to those in the literature, can be attributed to higher levels of uric acid and phosphorus that result in a higher concentration gradient.

To the best of our knowledge, there are no studies in the literature concerning the relationship of uric acid and phosphorus levels with the progression of ARF and response to therapy. However, there may be a relationship of the plasma concentrations of these two ions that causes tubular damage, as well as the duration of exposure to this high concentration with the severity of the disease and the response to the therapy. The highest uric acid level reported in the literature was 53 mg/dL in a TLS case.[4]

In our clinic, we performed sequential hemodialysis on a patient with TLS who had received ambulatory chemotherapy 2 days before his admission to the clinic due to T-ALL and was recommended for concomitant allopurinol (300 mg/day) and 3 L of oral hydration, but could not be sufficiently hydrated because of nausea, thus developing anuric ARF with a plasma uric acid level of 71.3 mg/dL. The presented patient, whose uric acid level was extremely high, was discharged after recovery by means of sequential hemodialysis sessions and sufficient hydration.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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