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A Rare Case of Spontaneous Tumor Lysis Syndrome in Idiopathic Primary Myelofibrosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 51
Final Diagnosis: Spontaneous tumor lysis syndrome • idiopathic primary myelofibrosis
Symptoms: Abdominal pain • general weakness
Medication: —
Clinical Procedure: Continuous renal replacement therapy • bone marrow biopsy
Specialty: Hematology

Objective: Rare disease

Background: Tumor lysis syndrome (TLS) is an oncologic emergency resulting from the massive destruction of tumor cells after cytotoxic chemotherapy for chemosensitive malignancies with a high tumor burden. Its clinical manifestations include severe electrolyte disturbances, metabolic acidosis, acute renal failure secondary to urate deposition in the kidney, heart, and skeletal muscle, and nervous system dysfunction. We report an extremely rare case of spontaneous TLS (STLS) in idiopathic primary myelofibrosis (PMF).

Case Report: A 51-year-old Korean man was admitted to our hospital with general weakness and left-side abdominal pain. The patient was diagnosed with acute urate nephropathy with hyperphosphatemia, hyperkalemia, hypocalcemia, and metabolic acidosis. Splenomegaly was accompanied by leukocytosis and a peripheral blood smear revealed immature granulocytes without blast cells. Bone marrow biopsy showed PMF. Initially, we presumed it was a spontaneous tumor lysis syndrome of PMF. We immediately performed emergency hemodialysis. We concluded that the patient, who had chronic hyperuricemia due to undiagnosed PMF, was recently admitted to the emergency room with STLS due to overwork and dehydration.

Conclusions: We present an extremely rare case of STLS in idiopathic PMF. The mechanism of chronic hyperuricemia in our case might be rapid cell turnover due to ineffective erythropoiesis of PMF.

MeSH Keywords: Primary Myelofibrosis • Tumor Lysis Syndrome • Uric Acid

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/912682

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Background

Acute renal failure rarely occurs in myeloproliferative neoplasms (MPN) such as primary myelofibrosis. The cause of acute renal failure in these cases is very diverse, including extramedullary hematopoiesis in renal or perirenal tissue, renal failure due to hyperuricemia, obstructive uropathy caused by urolithiasis, and extremely rare cases of spontaneous tumor lysis syndrome (STLS) [1–5].

Tumor lysis syndrome (TLS) is a metabolic emergency resulting from massive destruction of tumor cells and subsequent release of intracellular ions, nucleic acids, and protein breakdown products into the bloodstream. The accumulation of these substances in the blood may result in clinical abnormalities and aberrant laboratory results. TLS usually occurs after cytotoxic chemotherapy for hematologic malignancies (such as high-grade lymphomas, acute leukemias) and some chemosensitive solid cancers (such as small cell lung cancer). Its clinical manifestations include severe electrolyte disturbances (hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia), metabolic acidosis, acute renal failure secondary to urate deposition in the kidney, heart, and skeletal muscle, and nervous system dysfunction [6,7]. Spontaneous TLS (STLS) occurs prior to the initiation of cytotoxic therapy. It is extremely rare and is mostly observed in highly proliferative malignancies [8,9].

We report an extremely rare case of STLS in idiopathic primary myelofibrosis (PMF). To the best of our knowledge, there is only 1 reported case of STLS in PMF and it was published in 2001 [5].

Case Report

A 51-year-old Korean man was admitted to our hospital with general weakness and left-side abdominal pain. His medical history was unremarkable except for a 3-year history of hypertension. Physical examination showed splenomegaly 10 cm below the left costal margin, and abdominal radiology revealed an enlarged spleen (23 cm) (Figure 1). The arterial blood gas analysis (ABGA) on room air showed pH of 7.33, PaCO2 of 35.2 mmHg, PaO2 of 96.5 mmHg, HCO3– of 18.3 mEq/L, and base excess of -7.6. Laboratory findings showed a high white blood cell count (28.49×10^3/μL; 70.8% neutrophils and 11.1% lymphocytes), a hemoglobin level of 10.3 g/dL, and a platelet count of 920×10^3/μL. Levels of C-reactive protein (0.22 mg/dL) and procalcitonin (0.230 ng/mL) were within the normal ranges (0–0.3 mg/dL and 0–0.5 ng/mL, respectively). Liver function was normal. Serum sodium level (139 mEq/L) was normal, whereas serum potassium level (5.7 mEq/L) was elevated. Blood urea nitrogen (35 mg/dL) and creatinine (3.67 mg/dL) levels were also elevated. Calculated fractional excretion of sodium (2.3%) indicated renal-type or postrenal-type acute renal failure. Lactate dehydrogenase (1230 IU/L), phosphate (6.87 mg/dL), and uric acid (16.2 mg/dL) levels were elevated, whereas calcium (6.76 mg/dL) and ionized calcium (3.61 mg/dL) levels were low. The patient was diagnosed with acute urate nephropathy with hyperphosphatemia, hyperkalemia, hypocalcemia, and metabolic acidosis. Moreover, the above findings were similar to those in STLS (Table 1).

Splenomegaly was accompanied by leukocytosis, and a peripheral blood smear revealed immature granulocytes without blast cells. We presumed that the condition was STLS of hematologic malignancy.

On admission, the patient was considered to be dehydrated and we performed massive hydration. However, this progressed to general edema and he had less urination. To reduce the excess fluid, we administered diuretics and allopurinol. However, 2 days later, serum creatinine concentration increased to 5.40 mg/dL and urine output substantially decreased. We presumed that

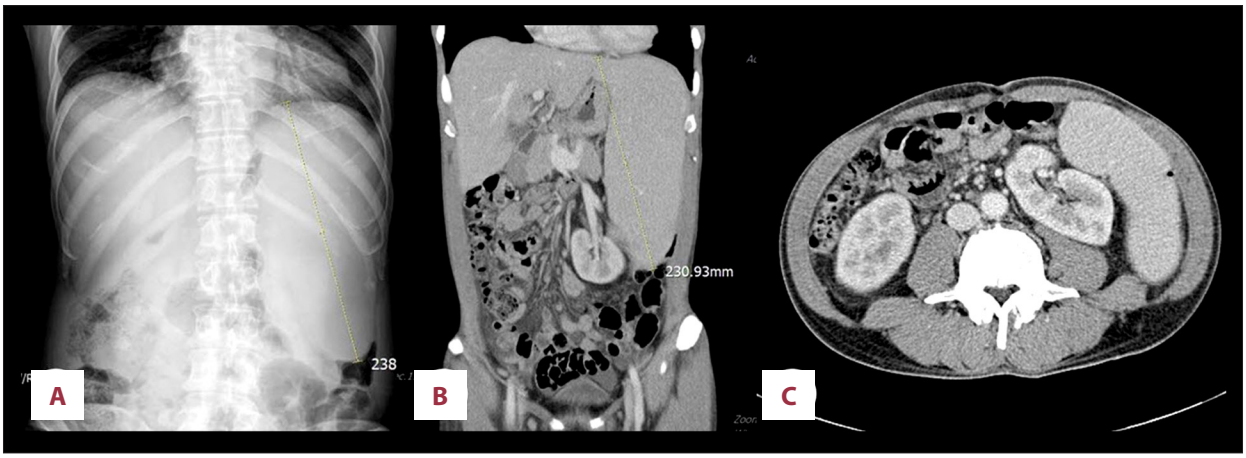

Figure 1. (**A**) Abdominal radiology revealed an enlarged spleen (23 cm). (**B, C**) Abdominal and pelvic computed tomography showed a greatly enlarged spleen (23×11 cm) without hydronephrosis and ureter obstruction sign.

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Table 1. Laboratory data at admission and follow-up.

Variable	Admission	HD #3	HD #7	HD #14	After 2 years	After 2 years 3 months
WBCs (×10³/μL)	28.49	26.05	16.51	11.16	13.33	19.900
Hb (g/dL)	10.3	10.6	10.1	10.3	9.0	8.5
Platelets (×10³/μL)	920	903	726	698	744	558
Sodium (mEq/L)	139	139	140	138	139	140
Potassium (mEq/L)	5.7	6.0	5.4	5.7	4.7	5.7
Bicarbonate (mmol/L)	17.9	18.8	–	27.8	26.3	
BUN (mg/dL)	35.0	43.0	22.7	26.8	33.9	39.4
Creatinine (mg/dL)	3.67	5.40	2.26	1.87	1.46	1.62
Calcium (mg/dL)	6.54	6.30	6.82	7.83	–	
Phosphate (mg/dL)	6.87	6.62	5.78	4.12	–	
Uric acid (mg/dL)	16.2	16.8	10.5	6.1	8.4	
LDH (U/L)	1230	1430	1110	1124	934	
Clinical course	Allopurinol Hydration Diuretics	Start Hemodialysis	Stop hemodialysis Start hydroxyurea	Discharge from hospital Allopurinol Hydroxyurea	Long-term follow-up	Start Ruxolitinib

WBC – white blood cell; Hb – hemoglobin; HD – hospital day; BUN – blood urea nitrogen; LDH – lactate dehydrogenase.

this was a case of STLS of hematologic malignancy; however, we were unable to administer rasburicase because of its scarcity and unavailability in our hospital. Hence, we immediately performed emergency hemodialysis. Post-hemodialysis abdominal and pelvic computed tomography showed a greatly enlarged spleen (23×11 cm) without hydronephrosis (Figure 1). Hemodialysis was continued daily for 4 consecutive days to normalize the electrolyte imbalance and decrease creatinine and uric acid levels.

We attempted a bone marrow biopsy, but it was difficult to aspirate the marrow (dry tap), thus, we could not examine the percentage of blasts in the bone marrow via cell counting. However, a bone marrow biopsy section revealed dense reticulin fibrosis with megakaryocytic proliferation and collagen fibrosis (MF-2 grade). Marrow cellularity was estimated to be 100% and *JAK2* V617F mutation was detected. The histopathological diagnosis was PMF (Figure 2). According to the 2016 revision to World Health Organization classification of myeloid neoplasm and acute leukemia, primary myelofibrosis is based on 3 major criteria: (1) The presence of megakaryocytic proliferation with grade collagen fibrosis; (2) Not meeting criteria for essential thrombocytosis, polycythemia vera, BCR-ABL positive chronic myeloid leukemia, and myelodysplastic syndrome; and (3) JAK2 positivity and at least 2 minor criteria (leukocytosis and splenomegaly). The patient was classified into the low-risk group of the Dynamic International Prognostic Scoring System-Plus (DIPSS-plus), which was zero. Usually, the main goal of therapy for low-risk PMF is symptom control alone, and the patient had massive splenomegaly. Symptom control was performed by the administration of hydroxyurea (500 mg/per day) for 7 consecutive days.

Finally, the patient was diagnosed with STLS in PMF. At the time of hospital discharge (14 consecutive days), serum creatinine concentration was 1.87 mg/dL and uric acid concentration was 6.1 mg/dL. Blood count showed a white blood cell count of 11.16×10³/L, a hemoglobin level of 10.3 g/dL, and a platelet count of 698×10³/L.

The patient continued to receive hydroxyurea (500 mg/per day) and allopurinol (300 mg/per day) daily. Blood counts and uric acid levels were well controlled and there were no splenomegaly-related symptoms during the 2 years after discharge, although the size of the spleen remained constant.

After 27 months, a PB smear showed 3% blasts, and a blood count showed progressive anemia (8.5 g/dL) with increased white blood cell count (19.90×10³/L), and a platelet count of 558×10³/L. Therefore, we repeated the bone marrow biopsy.

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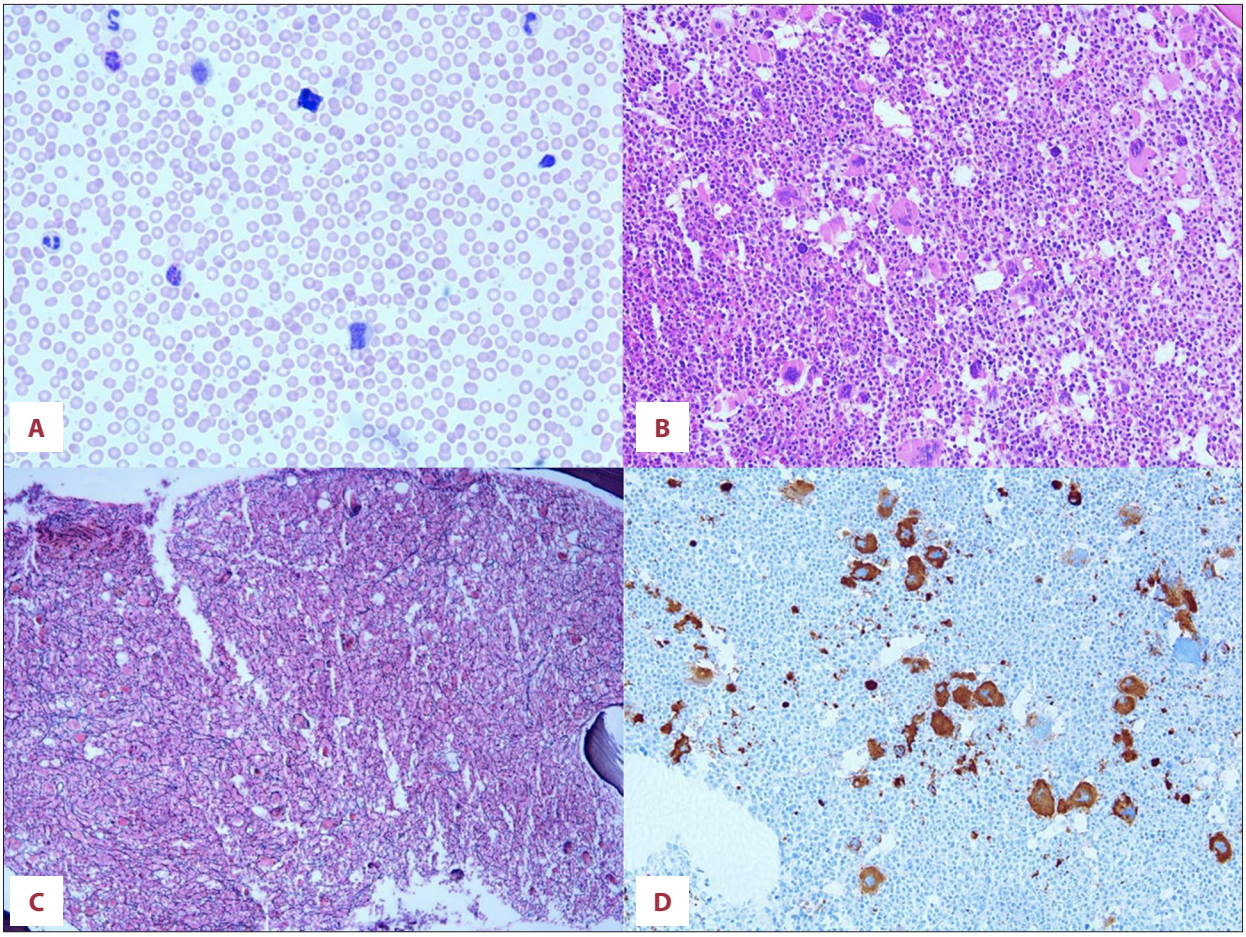

Figure 2. (**A**) Peripheral blood smear showed immature granulocytes without blasts (×400). (**B**) Bone marrow biopsy section revealed dense reticulin fibrosis with entrapped hematopoietic elements (megakaryocytes). Marrow cellularity was estimated to be nearly 100% (×400). (**C**) Reticular staining of the bone marrow section revealed dense reticulin fibrosis and collagen fibrosis (MF-2 grade) (×200). (**D**) Many proliferative megakaryocytes can be observed in the CD61 stained (×400) specimen.

The bone marrow showed 2% blast cells, although we could barely aspirate the marrow, and the bone marrow biopsy section was consistent with MF-3 grade primary myelofibrosis. We calculated the DIPSS-plus score again and the patient was categorized in the intermediate-2 risk group. He discontinued hydroxyurea and started ruxolitinib (a JAK2 inhibitor), which he is receiving to date.

Discussion

In the case presented herein, the patient was diagnosed with PMF and acute renal failure without hydronephrosis. Acute renal failure was indicated by hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and metabolic acidosis. Acute uric acid nephropathy, which could be defined by the TLS, was diagnosed.

Idiopathic PMF is considered a myeloproliferative disorder owing to the proliferation of fibrous connective tissue in the bone marrow. PMF is symptomatic of myelophthisic anemia with leukocytosis and/or thrombocytosis with hepatosplenomegaly because of extramedullary hematopoiesis [10,11]. Although various causes of acute renal failure in the MPN such as PMF may occur, the tumor lysis syndrome is not well known. However, the use of JAK2 inhibitors has been recently increasing, and TLS have been reported after drug administration [1,2,4,12]. Cairo and Bishop defined laboratory and clinical TLS by modifying the definitions proposed by Hande-Garrow. They defined laboratory TLS as abnormal levels of 2 or more of the following 3 days before or 7 days after treatment: uric acid, phosphate, potassium, and calcium. They defined clinical TLS as laboratory TLS occurring with 1 or more of these complications: renal failure, cardiac arrhythmia, seizure, and sudden death [6,7]. This definition also applies to TLS in the absence of chemotherapy (i.e., STLS). STLS is a rare

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disease that occurs prior to the initiation of cytotoxic therapy. Only a few cases have been reported, and in all, STLS was accompanied by highly aggressive lymphoid malignancies, usually those with a bulky mass [8,9].

It is well understood that the cause of increased cell turnover in PMF or any other MPNs is ineffective erythropoiesis that leads to cellular destruction and increased uric acid synthesis. Hyperuricemia in PMF or MPN sometimes causes gout or uric acid renal stones; however, acute renal failure or occlusive uropathy is rare [1,2]. Furthermore, to the best of our knowledge, there is only 1 previous case report like ours. Sile et al. reported that a 70-year-old man with an 18-month history of idiopathic myelofibrosis developed nonoliguric acute renal failure in association with acute uric acid nephropathy in the absence of chemotherapy or radiotherapy [5].

In summary, our patient was suspected to have hematologic malignancy due to massive splenomegaly and leukocytosis with immature granulocytes. Furthermore, he showed acute renal failure with hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis and was diagnosed with acute uric acid nephropathy, which could be defined by STLS. Initially, we presumed it was a spontaneous tumor lysis syndrome (STLS) of hematologic malignancy. Thus, in our case, we concluded that the patient, who had chronic hyperuricemia due to undiagnosed PMF, was recently admitted to the emergency room with acute uric acid nephropathy due to overwork and dehydration. The mechanism of chronic hyperuricemia in our patient might be rapid cell turnover due to ineffective erythropoiesis of PMF.

However, there has been no report of rapid and significant renal failure occurring with acute uric acid nephropathy requiring dialysis in the above-mentioned myeloproliferative disorders, especially in myelofibrosis.

Conclusions

STLS, although rare, can occur prior to the initiation of cytotoxic therapy, with most reports associating it with highly proliferative malignancies. We present an extremely rare case of STLS in PMF. To the best of our knowledge, this is the only the second case report of this disease.

Conflict of interest

None.

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