INTERNAL MEDICINE

□ CASE REPORT □

Tumor Lysis-like Syndrome in Eosinophilic Disease of the Lung: A Case Report and Review of the Literature

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Abstract

Tumor lysis syndrome (TLS) is a metabolic disorder that is generally associated with a malignancy leading to hyperuricemia, hyperphosphatemia, and acute kidney injury. On the other hand, we sometimes encounter these phenomena in nonmalignant disease, which has been referred to as tumor lysis-like syndrome in some studies. We herein experienced a case in which tumor lysis-like syndrome occurred in the course of therapy for eosinophilic disease of the lung, a nonmalignant disease. Even in nonmalignant disease, massive cell lysis induced by therapy can cause phenomena such as TLS or tumor lysis-like syndrome.

Key words: tumor lysis syndrome, eosinophilic disease of the lung, hypereosinophilia, nonmalignancy, chronic kidney disease, acute kidney injury

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Introduction

Tumor lysis syndrome (TLS) is a metabolic disorder caused by an exploding intracellular substance release that occurs when tumor cells lyse after the initiation of cytotoxic therapy (1). TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, metabolic abnormalities that can involve renal dysfunction, arrhythmia, and seizure (2). TLS is generally related to a hematologic malignancy or a solid tumor (3-6), however, the same pathological condition reportedly occurs in nonmalignant diseases (7-17) and is known as tumor lysis-like syndrome. We herein report a case in which a nonmalignant disease, eosinophilic disease of the lung, caused tumor lysis-like syndrome after steroid pulse therapy.

Case Report

A 77-year-old man who regularly visits our nephrology clinic for the treatment of diabetic nephropathy developed malaise for 3 days. His symptoms worsened and were accompanied by dyspnea and lethargy. Accordingly, he was transported to our hospital by ambulance and admitted.

His respiratory rate was 20/min and SpO_2 was 85% without oxygen administration. His consciousness level was E3V4M6 on the Glasgow Coma Scale. His blood pressure, heart rate, and body temperature were within normal limits. There were no abnormal physical findings other than moderate pitting edema on his lower legs. However, computed tomography (CT) showed a bilateral pleural effusion and consolidation dominant in the bilateral inferior lobe (Fig. 1a). His white blood cell (WBC) count was elevated to 16,100 cells/μL with an increased proportion of eosinophils (26%; 4,186 cells/μL) compared to 5.9% (=260 cells/μL) 2 years previous (latest available data on eosinophil count prior to this admission). His red blood cell and platelet counts were the same as his usual values. The serum creatinine level was 3.23 mg/dL, which was not elevated from his baseline value, while the C-reactive protein level was 5.2 mg/dL. His serum sodium, potassium, calcium, phosphate, bicarbonate, lactate dehydrogenase, and uric acid levels were basically within normal limits. He showed proteinuria of about 5 g/gCre without hematuria, and his serum albumin was 2.3 g/dL. Antineutrophil cytoplasmic antibody, antinuclear antibody, anti-glomerular basement membrane antibody, procalcitonin, and β-D-glucan tested negative. Echocardiography and electrocardiography examinations revealed no significant abnormalities.

We initially attributed his dyspnea to pulmonary edema

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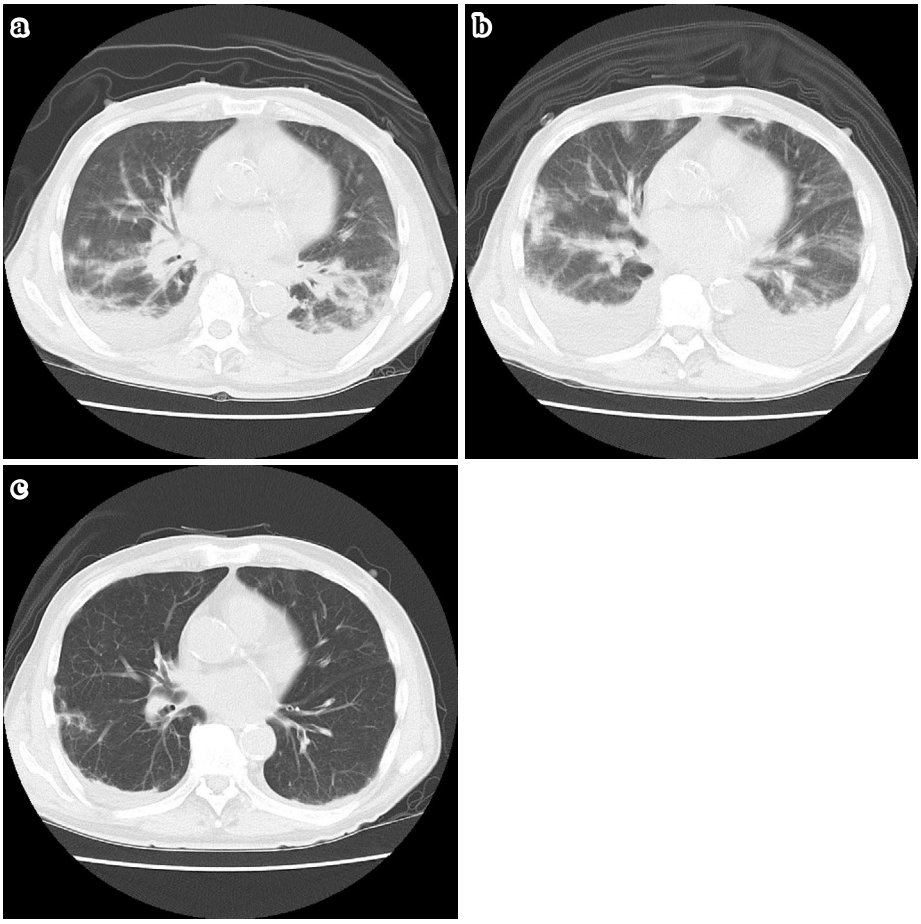

Figure 1. **a: A computed tomography image showing bilateral pleural effusion and consolidation dominant in the bilateral inferior lobe on admission (tested on the first day after admission). b: Despite the use of diuretics, pleural effusion and consolidation increased during the week after admission (tested on the fifth day after admission). c: Pleural effusion and consolidation had almost disappeared on the computed tomography image 2 weeks after steroid pulse therapy (tested on the 23rd day after admission).**

due to volume overload and administered diuretics, however, the treatment was ineffective. One week after admission, his chest X-ray and respiratory status worsened (Fig. 1b), and his eosinophil count also increased to 10,900 cells/μL. Although we did not perform a bronchoalveolar lavage because it could deteriorate his respiratory condition, sputum cytology showed eosinophilia. Thus, we diagnosed his pulmonary lesion as eosinophilic disease of the lung. He had no history of asthma, recent medication changes, recent smoking, or dust inhalation. No findings suggested a parasitic or fungal infection. Eosinophilic disease of the lung is occasionally secondary to a malignancy, such as chronic myeloid leukemia or chronic eosinophilic leukemia. A bone marrow biopsy was performed to differentiate the malignant disease, and no blast increase, monoclonal proliferation, or chromosome abnormalities (including BCR-ABL fusion and FIPIL1-PDGFRA fusion) were found.

We administered methylprednisolone 500 mg/day intravenously for 3 days. His eosinophil cell count decreased to 0 cells/μL, and both the shortness of breath and chest consolidation resolved on the second day of steroid pulse therapy. However, his uric acid level became elevated to 14.8 mg/dL on the third day of therapy. His serum creatinine and phosphate levels also increased from 3.70 mg/dL to 4.47 mg/dL and from 4.5 mg/dL to 8.4 mg/dL, respectively, while his corrected calcium decreased from 9.2 mg/dL to 8.5 mg/dL (Table 1). Hyperuricemia (>8.0 mg/dL) and hyperphosphatemia (>4.5 mg/dL) met the laboratory criteria for TLS. Additionally, AKI (increase in the serum creatinine level of 0.3 mg/dL) met the clinical criteria for TLS (3), while no arrhythmia, seizure, nausea, lethargy or tetany was seen. Accordingly, we presumed that the patient had a condition such as TLS.

Rasburicase 7.5 mg with hydration was administered. Oliguria caused temporary volume overload, however, his urinary volume increased in response to hydration and his creatinine level started to decrease. Hemodialysis was not required in the treatment course. The pleural effusion and consolidation had almost disappeared on CT 2 weeks after steroid pulse therapy (Fig. 1c). The dyspnea resolved and his SpO_2 remained at 97% without oxygen administration. The patient was discharged from the hospital 1 month after

Table 1. Laboratory Data Examining Steroid Pulse Efficacy.

	On admission (day 2)	Before steroid pulse (day 8)	After steroid pulse (day 11)	Two weeks after steroid pulse (day 24)
WBC (cells/μL)	16,100	20,000	7,500	7,600
Eosinophil (cells/μL)	4,186	10,900	0	228
Creatinine (mg/dL)	3.23	3.70	4.47	3.09
Uric acid (mg/dL)	5.2	8.3	14.8	6.1
Phosphate (mg/dL)	3.7	4.5	8.4	3.4
Corrected calcium (mg/dL)	9.0	9.2	8.5	8.6
Potassium (mEq/L)	5.5	4.5	4.9	4.4
Lactate dehydrogenase(U/L)	266	334	202	224
pH	7.322	7.336	7.330	-
Bicarbonate (mEq/L)	22.6	24.6	22.1	-
Urinary pH	6.0	6.0	5.5	6.0
Brain natriuretic peptide (pg/mL)	485.0	252.0	459.0	156.5

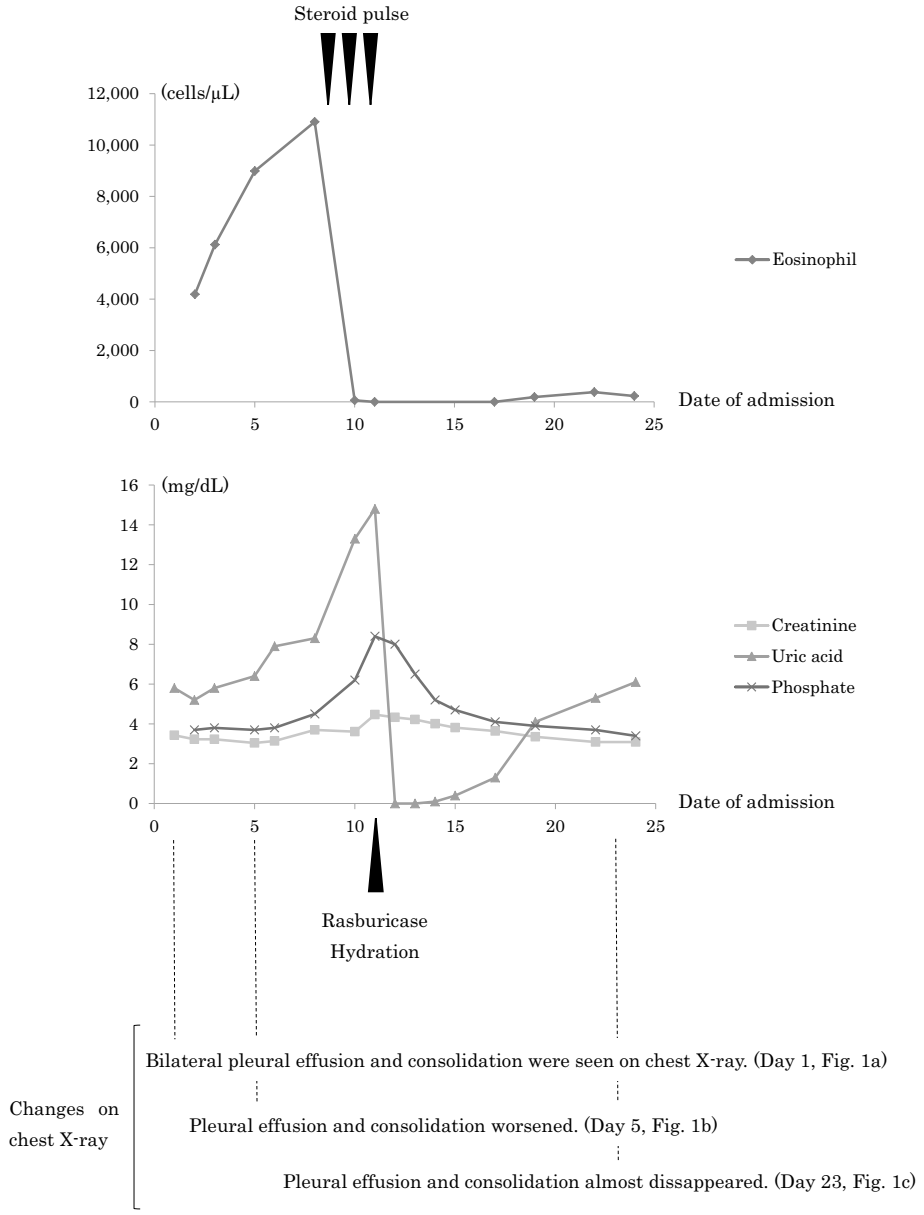

Figure 2. The eosinophil count dropped immediately after steroid pulse therapy. The serum creatinine, uric acid, and phosphate levels decreased quickly after the administration of rasburicase.

Table 2. Tumor Lysis-like Syndrome in Nonmalignant Diseases.

Primary disease	Reference	Age, sex	Trigger	Treatment	Outcome
Visceral leishmaniasis	(7)	Age: 22y-73y, 7males, 4females	Liposomal amphotericin B	Hydration, alkalization, allopurinol	IP and BUN of all patients got normal. Cre and uric acid of 20% and 30% of patients remained high. (30 days after the initiation of therapy)
Multicentric Castleman's disease	(8)	34y, male	Spontaneous Cyclophosphamide+prednisone	Hemodialysis, allopurinol	Renal function slowly improved over 6 weeks.
	(9)	44y, male	Spontaneous CHOP chemotherapy	Hemodialysis, hydration, alkalization	Creatinine got normal at discharge. (57 days after the initiation of therapy.)
	(10)	33y, male	CVP (prednisolone, vincristine, cyclophosphamide) + dexamethasone	Hydration, alkalization, diuretic, hemodialysis	Death on chemotherapy day 17.
	(11)	13y, male	Methylprednisolone	Hydration, rasburicase	Renal function normalized over the next several days.
Langerhans cell histiocytosis	(12)	8m, female	VP (prednisolone, vincristine)	Hydration, alkalization, allopurinol, diuretic, hemofiltration	Laboratory abnormalities improved. (the date and the duration period were not specified.)
Infantile hemangioma	(13)	33d, female	Propranolol	No specific treatment	Serum K and P levels remained elevated until the third month of therapy. creatinine and uric acid remaind normal during the course.
Transient abnormal myelopoiesis	(14)	1d, female	Spontaneous	Hydration, alkalization, allopurinol, diuretic	Metabolic parameters were normalized in several days.
	(15)	1d, male	Spontaneous	Peritoneal dialysis	Death at the age of 5 days.
Myelodysplasia	(16)	32y, male	Methylprednisolone	Hemodialysis	Renal function recovered 1 week later.
	(17)	53y, male	Spontaneous	Hemodialysis	Serum Creatinine almost returned to normal 2 weeks later.

this admission. The clinical course is summarized in Fig. 2.

Discussion

To the best of our knowledge, this is the first reported case in which a metabolic disorder and a clinical manifestation similar to TLS resulted from eosinophilic disease of the lung. Although TLS is related to a hematologic malignancy or a solid tumor in most cases, this case showed that the same pathological condition as TLS can occur in the presence of a nonmalignant disease, which we hereafter refer to as tumor lysis-like syndrome, and prophylactic measures should be considered for a patient with risk factors for TLS.

Some case reports have shown that tumor lysis-like syndrome occurs in other nonmalignant diseases (7-17) (Table 2). Various nonmalignant diseases that have the potential risk of mass burden can cause tumor lysis-like syndrome. The therapies conducted for tumor lysis-like syndrome in these nonmalignant diseases were the same as those for TLS in the presence of malignant disease and included hydration, alkalization, allopurinol, diuretics, and dialysis. Since only a few reported cases with each disease have so far been reported, we cannot identify the risk factors associated with the prognosis.

Despite the absence of a malignancy, this patient actually had several other risk factors for TLS. His serum creatinine level was 3.70 mg/dL before the initiation of therapy, and the renal dysfunction could have contributed to the onset of tumor lysis-like syndrome (18). Dehydration is another risk factor for TLS (19), and the patient was possibly dehydrated because we had attributed his dyspnea to volume overload and had administered diuretics. A rapid proliferating rate and elevated WBC count can also precipitate TLS; in fact, a panel of experts recommended that a patient with a WBC count >10,000 cells/μL be classified as at intermediate risk for TLS in acute myeloid leukemia and chronic lymphocytic leukemia (20). In the present case, the WBC count peaked at 20,000 cells/μL (eosinophil 10,900 cells/μL) before steroid therapy was started, and doubled within a few days, indicating a high proliferating rate. Effective steroid pulse therapy also could have played a role in the onset of tumor lysis-like syndrome (16, 18-28). Steroids induce eosinophil

apoptosis through the direct promotion of apoptotic cascades, suppression of the synthesis and effects of eosinophil survival factors, and the stimulation of their engulfment by phagocytes (29, 30). The patient's eosinophil count decreased from 10,900 cells/μL to 0 cells/μL in a single day, while rapid eosinophil apoptosis released huge quantities of toxic intracellular substances within a short amount of time.

To the best of our knowledge, this is the first case where rasburicase was administered to treat tumor lysis-like syndrome caused by a nonmalignant disease. The patient's hyperuricemia, hyperphosphatemia, and AKI were caused by the rapid release of intracellular substances after the collapse of a substantial amount of cells, which is the same pathology as TLS in malignancy. Moreover, the patient had a high risk of severe AKI because of renal insufficiency before the onset of tumor lysis-like syndrome, and rasburicase is reported to be superior to allopurinol in the rapid recovery of serum creatinine elevation in TLS (31). That is why we decided to use rasburicase in this case after a consensus in our department, although rasburicase is indicated for use only in TLS associated with chemotherapy for a malignancy in Japan. Indeed, rasburicase rapidly reduced the serum uric acid and creatinine levels in our case.

TLS is almost always associated with a malignancy, and we seldom predict its occurrence with a nonmalignant disease. Nevertheless, some nonmalignant diseases indeed cause the same metabolic disorders and clinical manifestations as TLS in the presence of other risk factors. Thus, prophylactic measures should be considered when encountering a patient with risk factors for TLS, even in the presence of a nonmalignant disease.

The authors state that they have no Conflict of Interest (COI).

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