

Successful Intensive Care Treatment of Severe Lactic Acidosis and Tumor Lysis Syndrome Related to Intravascular Lymphoma

Hiroshi Mase^{1,2}, Yutaro Ogawa¹, Jumpei Takeuchi¹,
Yuki Genda^{1,2}, Shingo Ichiba² and Atsuhiko Sakamoto¹

¹Department of Anesthesiology, Nippon Medical School, Tokyo, Japan

²Department of Surgical Intensive Care, Nippon Medical School, Tokyo, Japan

Intravascular lymphoma is a rare disease that progresses to multiple organ dysfunction caused primarily by tumor cell proliferation in small blood vessels. Few studies have investigated critical care management of intravascular lymphoma. We describe a rare case of multiple organ failure due to intravascular lymphoma with severe lactic acidosis in a patient who survived. A 64-year-old man with impaired consciousness was diagnosed as having intravascular large B-cell lymphoma by means of a random skin biopsy. The patient arrived at our hospital's intensive care unit (ICU) with impaired consciousness, respiratory failure that required mechanical ventilation, and lactic acidosis that required renal replacement therapy. Mechanical ventilation and renal replacement therapy were continued in the ICU, and his respiratory status and circulatory dynamics eventually stabilized. However, his impaired consciousness and hyperlactatemia did not improve until after the start of chemotherapy with doxorubicin, cyclophosphamide, vincristine, prednisolone, and rituximab. Although he developed tumor lysis syndrome immediately after chemotherapy, his systemic condition was gradually stabilized by continued critical care management primarily comprising renal replacement therapy. He was weaned from ventilator support after a tracheotomy and moved to the general ward. Hematopoietic malignancy with hyperlactatemia has a very poor prognosis; however, hyperlactatemia and impaired consciousness were dramatically improved in this patient by critical care management and chemotherapy.

(J Nippon Med Sch 2020; 87: 32–36)

Key words: lymphoma, lactic acidosis, renal replacement therapy, chemotherapy, critical care

Introduction

Intravascular lymphoma is a rare disease that typically involves multiple organ dysfunction, including dysfunction of the central nervous system, caused primarily by proliferation of tumor cells in small blood vessels. The rapid progression of the disease complicates antemortem diagnosis, and few studies have described successful critical care management of patients with multiple organ failure caused by intravascular lymphoma. We describe a case of multiple organ failure caused by lymphoma with severe lactic acidosis in a patient who clinically improved after critical care management and chemotherapy in an intensive care unit (ICU).

Case Presentation

A 64-year-old man with impaired consciousness was transported to a hospital by ambulance. His medical history was unremarkable, and cranial computed tomography scanning and magnetic resonance imaging performed just after arrival revealed no intracranial abnormalities. Extensive medical evaluation, blood testing, and imaging studies by the medical team at the previous hospital ruled out a number of diseases as the cause of impaired consciousness. Herpes encephalitis was a suspected cause of impaired consciousness. Because delayed treatment for herpes encephalitis leads to poor outcomes, he was admitted to hospital for additional treatment. Af-

Correspondence to Hiroshi Mase, MD, PhD, Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

E-mail: hiroshi-m@nms.ac.jp

https://doi.org/10.1272/jnms.JNMS.2019_86-606

Journal Website (<https://www.nms.ac.jp/sh/jnms/>)

Table 1 Patient characteristics on ICU admission.

Respiratory physiology	
Minute ventilation (L/min)	12
FiO ₂	0.6
Driving pressure (cmH ₂ O)	15
PEEP (cmH ₂ O)	10
PaO ₂ /FiO ₂ ratio	187
pH	7.181
PaCO ₂ (mmHg)	37.1
Bicarbonate (mmol/L)	20.5
Base excess (mEq/L)	-4.2
Lactate (mmol/L)	14.1
Alveolar-arterial oxygen difference (mmHg)	311
Additional physiology and laboratories	
Glasgow Coma Scale	E3VtM1
Body temperature (°C)	37.7
Systolic blood pressure (mmHg)	143
Mean arterial pressure (mmHg)	104
Heart rate (beats/min)	86
Respiratory rate (/min)	25
White blood cells (/μL)	4,000
Hemoglobin (g/dL)	10.7
Hematocrit (%)	32.5
Platelets (10 ⁴ /μL)	5.6
Sodium (mEq/L)	145
Potassium (mEq/L)	3.5
Bilirubin (mg/dL)	1.2
Creatinine (mg/dL)	0.85
Twenty-four-hour urine output (mL)	250
Glucose (mg/dL)	93
Left ventricular ejection fraction (%; by echocardiography)	67
Severity score	
Acute physiologic assessment and chronic health evaluation II (APACHE II)	38
Second simplified acute physiology score (SAPS II)	89
Sequential organ failure assessment (SOFA) score	18

ICU, intensive care unit; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PaO₂, partial pressure of arterial oxygen; PaCO₂, partial pressure of arterial carbon dioxide; APACHE II, acute physiologic assessment and chronic health evaluation II; SAPS II, second simplified acute physiology score; SOFA, sequential organ failure assessment

ter treatment, his consciousness remained impaired. Malignant lymphoma was suspected as a cause of impaired consciousness by the previous medical team, which noted an elevated serum soluble interleukin-2 receptor (sIL-2R) level of 11,400 U/mL. Later, intravascular large B-cell lymphoma was diagnosed after pathological examination of a random skin biopsy.

On the tenth day of hospitalization, he was placed on mechanical ventilation because of his rapidly deteriorating respiratory condition. Concurrent renal replacement therapy was started because of oliguria and prominent lactic acidosis. Intermittent renal replacement therapy and high-flow continuous hemodiafiltration were performed for treatment of prominent lactic acidosis. Although the dialysate flow rate of continuous renal replacement therapy was increased to 1,800 mL/h, lactic acidosis did not improve. Intermittent renal replacement therapy was conducted daily, and sodium bicarbonate was administered continuously. Although the patient had been scheduled for transfer to the hematology department to receive chemotherapy for his primary disease, he was instead admitted to the ICU for mechanical ventilation and renal replacement therapy.

The **Table 1** shows the patient's respiratory, physiological, and laboratory findings and initial severity score on ICU admission. The level of partial pressure of arterial oxygen was 112 mm Hg, the ratio of partial pressure of arterial oxygen/fraction of inspired oxygen was 187, serum lactate level was 14.1 mmol/L, and his level of consciousness, according to his Glasgow Coma Scale (GCS), was E3VtM1. In the ICU, the patient received pressure-controlled ventilation at an inspiratory driving pressure of 10 to 15 cm H₂O, a positive end-expiratory pressure of 5 to 10 cm H₂O, and a fraction of inspired oxygen of 0.25 to 0.6. In addition, blood flow rate was set to 80 mL/min, and dialysate flow rate was set to a maximum of 1,200 mL/h for continuous renal replacement therapy. Respiratory condition and circulatory dynamics stabilized, and acidosis improved; however, his level of consciousness (GCS E3VtM1) and hyperlactatemia did not change. Intermittent renal replacement therapy and sodium bicarbonate administration were thus terminated.

On the second day in the ICU, his temperature rose to 38.5°C and blood pressure dropped. Septic shock was suspected, and broad-spectrum antimicrobial and antifungal agents were administered. A circulatory agonist was administered temporarily, and culture tests were performed. The possibility of infection was excluded by negative results on all tests.

The **Figure 1** shows the patient's clinical course from the time of admission to the ICU. Although chemotherapy is associated with a high risk of organ dysfunction, the absence of other effective treatments led us to administer chemotherapy on the seventh day in the ICU. The chemotherapy regimen comprised doxorubicin 50 mg/m², cyclophosphamide 750 mg/m², and vincristine 1.4 mg/m²

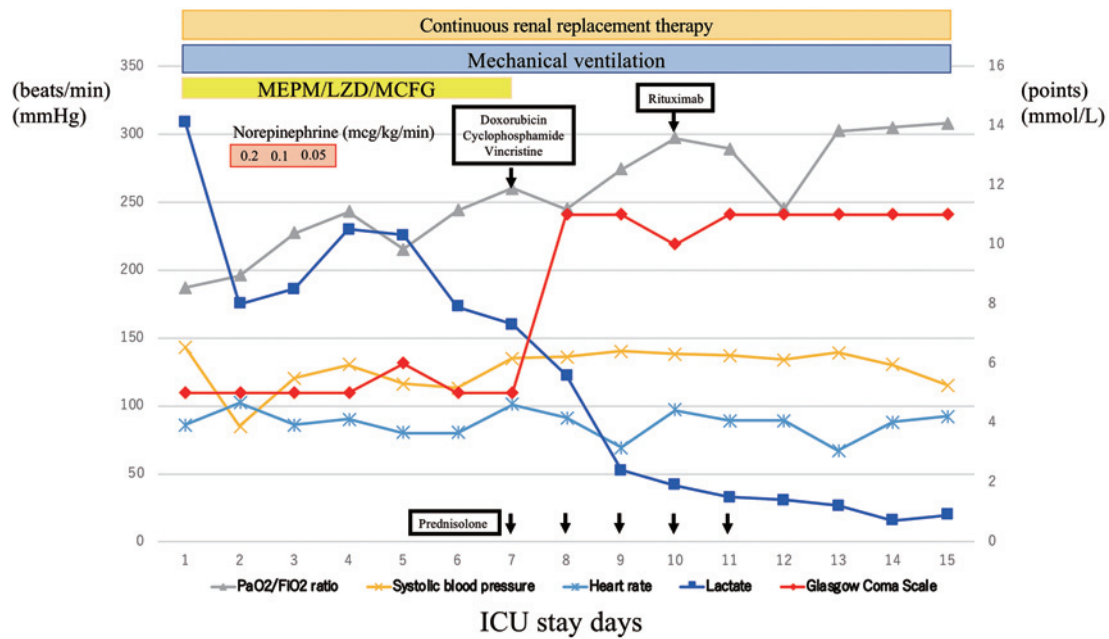


Fig. 1 The patient's clinical course after transfer to the ICU.

Mechanical ventilation support and continuous renal replacement therapy were continued for treatment of respiratory failure and severe lactic acidosis, respectively. Although respiratory condition and circulatory dynamics stabilized, and acidosis improved, consciousness level and hyperlactatemia were unchanged. Chemotherapy was started on the seventh day in the ICU. A significant improvement in the level of consciousness (Glasgow Coma Scale) was observed on the second day of chemotherapy. Serum lactate level significantly decreased and then normalized 2 days after beginning chemotherapy.

ICU, intensive care unit; MEPM, meropenem; LZD, linezolid; MCFG, micafungin; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen

on day 1, prednisolone 100 mg/day on days 1 through 5, and rituximab 600 mg on day 4. Level of consciousness was significantly better (GCS, E4VtM6) on the second day of chemotherapy, and serum lactate level was significantly better on the following day. Serum lactate level decreased to 1.9 mmol/L on the fourth day of chemotherapy.

The patient developed disseminated intravascular coagulation syndrome associated with tumor collapse immediately after completion of chemotherapy and therefore remained in the ICU. His general condition gradually improved. Renal replacement therapy was resumed because of a transient decrease in renal function, which seemed to be caused by tumor lysis syndrome after chemotherapy. His renal function gradually improved, and urination became normal. On the sixteenth day in the ICU, renal replacement therapy was again discontinued. He was weaned from ventilator support after undergoing a tracheotomy and moved from the ICU to the general ward. Lumbar puncture was performed because we suspected that central nervous system invasion by tumor cells was the cause of his impaired consciousness. However, a definitive pathological diagnosis of central nerv-

ous system invasion was not possible. Three weeks after the first chemotherapy regimen, we administered doxorubicin 50 mg/m², cyclophosphamide 750 mg/m², and vincristine 1.4 mg/m² on day 1, and prednisolone 100 mg/day on days 1 through 5 as second-line chemotherapy. In addition, a total of three weekly rituximab treatments (400 mg/week) were administered from the twenty-third day after the second chemotherapy regimen. His overall condition improved. His serum sIL-2R level, which was 16,963 U/mL at the time of hospitalization, decreased to 2,745 U/mL just before transfer to another hospital. His clinical condition was stable and, on the 77th day, his symptoms were in remission and he was transferred to another hospital. Written informed consent was obtained from the patient for publication of this case report.

Discussion

The present patient had refractory hyperlactatemia that could not be normalized by powerful blood purification therapy. At a previous hospital, the patient was treated with concurrent intermittent blood purification and high-flow continuous hemodiafiltration. Severe lactic acidosis

was diagnosed as a pathological condition in this patient, and he was treated by potent blood purification therapy while maintaining acid-base balance. When lactic acidosis is associated with malignant lymphoma, as in this case, an elevated lactic acid level (>5 mmol/L) and lactic acidosis are observed in 15% and 1.8%, respectively, of patients with hematological malignancies¹⁻³. Only one other case of lactic acidosis accompanying intravascular lymphoma has been reported. Ours is the first of a patient who survived.

Lactic acidosis is classified as Type A or B. Type A lactic acidosis is characterized by hypoxemia, while Type B lactic acidosis is diagnosed in the absence of clinical evidence of hypoxemia and is associated with systemic diseases such as renal or hepatic failure and diabetes. Type A lactic acidosis is associated with ischemic bowel syndrome, sepsis, cardiogenic shock, and advanced dehydration, is most frequently seen in cases of tissue hypoperfusion, and is attributed to shock or cardiopulmonary arrest. Causes of Type B lactic acidosis include hematological malignancy, human immunodeficiency virus infection, diabetes, liver disease, vitamin B1 deficiency, mitochondrial disease, and biguanide drugs⁴.

The present patient required mechanical ventilation support for respiratory failure exacerbated by hypoxemia. The clinical course at the time of tracheal intubation suggested pneumonia, pulmonary embolism, and congestive heart failure as causes of respiratory failure. However, these conditions were excluded on the basis of culture tests and imaging and echocardiography findings. Noncardiogenic pulmonary edema was believed to be the main cause of respiratory failure, because water balance management by renal replacement therapy improved the patient's physical status. However, even after improvement in hypoxemia, acidosis did not improve. Acidosis was thus classified as Type B lactic acidosis. Immediately after transfer to the ICU in our hospital, the possibility of intestinal ischemia was excluded by contrast computed. During initial treatment in the ICU, broad-spectrum antimicrobial and antifungal drugs were administered simultaneously for suspected septic shock, which was later excluded on the basis of negative culture results.

When the diseases responsible for lactic acidosis are classified according to the mechanism of lactic acid elevation, there are conditions that increase lactic acid production, such as pheochromocytoma, respiratory alkalosis, and glycogenosis type 1, and diseases that decrease turnover of lactic acid, such as alcohol polydipsia and liver

disease. There are also medical conditions for which the detailed mechanisms of lactic acid elevation are unknown, such as malignant tumor, acquired immunodeficiency syndrome (human immunodeficiency virus infection), and hypoglycemia⁵.

Only one other case report has described lactic acidosis caused by intravascular lymphoma⁶; however, it did not detail the mechanism responsible for lactate elevation. The Warburg effect—ie, the increase in the rate of glucose uptake and preferential production of lactate in malignant tumor cells, even in the presence of oxygen—is a known cause of lactic acidosis and hypoglycemia in patients with malignant tumors. In tumor hypoxia, accumulation of hypoxia inducible factor-1 α is increased in cells. This leads to overexpression of glucose transporters/glycolytic enzymes and suppression of mitochondria metabolism, resulting in increased glucose uptake and excessive lactic acid production¹⁷. However, hypoglycemia was not observed in this case.

In cancer patients, lactic acidosis has an even worse prognosis, with a mortality rate of $>80\%$ ⁸. Chemotherapy is contraindicated in some cases, because of declining physical status or poor general health. However, no patient with intravascular lymphoma has improved without chemotherapy, as it is the only lifesaving treatment^{2,6}.

Determining the optimal chemotherapy regimen for administration during renal replacement therapy is often difficult. Moreover, the regimen selected differs in relation to the type of blood purification therapy, ie, if it is intermittent or continuous renal replacement therapy. Because our patient developed significant hyperlactatemia, continuous renal replacement therapy was performed before chemotherapy and was continued even after chemotherapy. When planning concurrent chemotherapy and blood purification therapy, the patient's age and physical status should be considered, as should the ability of the drug to be administered during dialysis, dosage, and the timing of blood purification therapy^{9,10}. Intermittent blood purification is associated with accumulation of toxicity and fluid retention on days without dialysis. In contrast, continuous renal replacement therapy, frequently performed in ICUs, provides constant dialysis performance and management of body fluids, even though the efficiency of dialysis and substance removal is inferior to that of intermittent blood purification. Design of a combined regimen of continuous renal replacement therapy and chemotherapy is easier; furthermore, this type of renal replacement therapy is a highly effective blood purification therapy. The present patient was an ideal candi-

date for this type of renal replacement therapy.

Tumor lysis syndrome—a serious complication that leads to acute renal failure and electrolyte abnormalities, mainly in the acute phase of hematopoietic neoplastic disease or immediately after chemotherapy—eventually leads to multiple organ dysfunction¹¹. This syndrome requires immediate treatment because disintegration of tumor cells proceeds rapidly and intracellular substances such as uric acid flowing into blood obstruct renal tubules, leading to renal failure. Active administration of continuous renal replacement therapy compensates for renal dysfunction as part of early treatment for tumor lysis syndrome and enables continuation of chemotherapy and eventual recovery from renal dysfunction¹¹. In our patient, it was difficult to normalize blood lactate levels by using blood purification in the ICU. However, renal replacement therapy was performed before chemotherapy and was continued after chemotherapy for acute renal failure accompanying tumor collapse. The patient's renal function gradually improved, which eliminated the need for blood purification. The patient was able to avoid chronic dialysis and was discharged.

In summary, this is a rare case in which lactic acidosis and impaired consciousness were significantly improved by critical care management and chemotherapy, allowing the patient to survive. Notably, critical care management centered on renal replacement therapy may enable chemotherapy in the ICU and lead to good clinical outcomes.

Conflict of Interest: The authors declare no conflicts of interest.

References

1. Romero-Garcia S, Lopez-Gonzalez JS, Báez-Viveros JL, Aguilar-Cazares D, Prado-Garcia H. Tumor cell metabolism: an integral view. *Cancer Biol Ther.* 2011;12:939–48.
2. De Raes EA, Benoit DD, Depuydt PO, et al. Early recognition of malignant lactic acidosis in clinical practice: report on 6 patients with haematological malignancies. *Acta Clin Belg.* 2012;67:347–51.
3. Elhomsy GC, Eranki V, Albert SG, et al. “Hyper-warburgism,” a cause of asymptomatic hypoglycemia with lactic acidosis in a patient with non-Hodgkin’s lymphoma. *J Clin Endocrinol Metab.* 2012;97:4311–6.
4. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med.* 2005;20:255–71.
5. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc.* 2013;88:1127–40.
6. Ronny FMH, Black MA, Arbini AA. Intravascular large B-cell lymphoma with multi-organ failure presenting as a pancreatic mass: a case with atypical presentation and definite diagnosis postmortem. *Autops Case Rep.* 2017;7:30–6.
7. Bhalla S, Evens AM, Prachand S, Schumacker PT, Gordon LI. Paradoxical regulation of hypoxia inducible factor-1 α (HIF-1 α) by histone deacetylase inhibitor in diffuse large B-cell lymphoma. *PLoS One.* 2013;8:e81333.
8. Martinez-Outschoorn UE, Whitaker-Menezes D, Valsecchi M, et al. Reverse Warburg effect in a patient with aggressive B-cell lymphoma: is lactic acidosis a paraneoplastic syndrome? *Semin Oncol.* 2013;40:403–18.
9. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol.* 2010;21:1395–403.
10. Niscola P, Vischini G, Tendas A, et al. Management of hematological malignancies in patients affected by renal failure. *Expert Rev Anticancer Ther.* 2011;11:415–32.
11. Choi KA, Lee JE, Kim YG, et al. Efficacy of continuous venovenous hemofiltration with chemotherapy in patients with Burkitt lymphoma and leukemia at high risk of tumor lysis syndrome. *Ann Hematol.* 2009;88:639–45.

(Received, January 26, 2019)

(Accepted, June 26, 2019)

(J-STAGE Advance Publication, July 15, 2019)