Successful treatment of severe lactic acidosis and tumor lysis syndrome related to intravascular lymphoma in the intensive care unit

Running title: ICU treatment of lactic acidosis in IVL

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Abstract

Intravascular lymphoma is a rare disease exhibiting multiple organ dysfunction, mainly due to tumor cell proliferation in small blood vessels. Few reports exist on the critical care management of intravascular lymphoma. We describe a rare case of multiple organ failure due to intravascular lymphoma with severe lactic acidosis wherein the patient survived. A 64-year-old man had impaired consciousness and was diagnosed with intravascular large B-cell lymphoma through 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. His mechanical ventilation and renal replacement therapy continued in the ICU and eventually his respiratory status and circulatory dynamics stabilized. However, his level of consciousness and hyperlactatemia did not improve until after doxorubicin, cyclophosphamide, vincristine, prednisolone, and rituximab chemotherapy. Although he experienced tumor lysis syndrome immediately after chemotherapy, his systemic condition gradually stabilized through continued critical care management consisting primarily of renal replacement therapy. He was weaned from ventilator support after undergoing a tracheotomy and moved into the general ward. Hematopoietic malignancies with hyperlactatemia have very poor prognosis; however, this patient’s hyperlactatemia and level of consciousness were dramatically improved by the critical care management and chemotherapy. We report a rare case in which a patient with intravascular lymphoma involving multiple organ failure survived.
Keywords
lymphoma, lactic acidosis, renal replacement therapy, chemotherapy, critical care
**Introduction**

Intravascular lymphoma is a rare disease that exhibits multiple organ dysfunction, including dysfunction of the central nervous system, caused primarily by the proliferation of tumor cells in small blood vessels. The rapid progression of the disease makes it difficult to reach an antemortem diagnosis. The reports on successful critical care management of patients with multiple organ failure caused by intravascular lymphoma are limited. We describe a patient with multiple organ failure caused by lymphoma with severe lactic acidosis who demonstrated clinical improvement through critical care management and chemotherapy at an intensive care unit (ICU).

**Case Presentation**

A 64-year-old man with impaired consciousness was transported to a hospital by ambulance. He had no remarkable medical history. A head computed tomography scan and magnetic resonance imaging performed just after arrival revealed no abnormalities of the intracranium. The previous medical team ruled out various diseases as the cause of his impaired consciousness through extensive medical evaluations, blood testing, and imaging studies. Herpes encephalitis was suspected as one of the causes of his impaired consciousness. Because delayed treatment for herpes encephalitis leads to poor prognosis, he was admitted to the hospital for additional treatment. After the treatment, his impaired consciousness continued without any sign of improvement. In addition, malignant lymphoma was suspected as one of the causes of his impaired consciousness by the previous medical team. They measured his serum soluble interleukin-2 receptor
(sIL-2R) level, which was 11,400 U/mL, and therefore above normal. Later, he was diagnosed with intravascular large B-cell lymphoma through pathological examination of a random skin biopsy.

On his tenth day in the hospital, he was placed on mechanical ventilation due to his rapidly degenerating respiratory condition. Simultaneously, renal replacement therapy was commenced due to oliguria and prominent lactic acidosis. Intermittent renal replacement therapy and high flow continuous hemodiafiltration were performed as treatment for prominent lactic acidosis. The dialysate flow rate of continuous renal replacement therapy was increased to 1800 mL/h; however, his lactic acidosis did not improve. Intermittent renal replacement therapy was conducted daily, and sodium bicarbonate was administered continuously. Although the patient was initially supposed to be transferred to the Department of Hematology to receive chemotherapy for his primary disease, he was instead admitted to the ICU due to the necessity for mechanical ventilation and renal replacement therapy.

The patient’s respiratory physiology, additional physiology and laboratories, and initial severity score upon ICU admission are shown in Table 1. The level of partial pressure of arterial oxygen was 112 mmHg, the ratio of partial pressure of arterial oxygen/fraction of inspired oxygen was 187, the 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, the blood
flow rate was set at 80 mL/min, and the dialysate flow rate was set at a maximum of 1200 mL/h for continuous renal replacement therapy. As a result, his respiratory condition and circulatory dynamics stabilized, and the level of acidosis improved; however, his level of consciousness (GCS E3VtM1) and hyperlactatemia did not change. Therefore, intermittent renal replacement therapy was terminated, and sodium bicarbonate was no longer administered.

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

Figure 1 shows the patient’s clinical course from the time of admission to the ICU. Although the patient had a high risk of developing organ dysfunction with chemotherapy, we decided to administer chemotherapy on the seventh day in the ICU because there was no other effective treatment. Chemotherapy was administered as follows: doxorubicin 50 mg/m², cyclophosphamide 750 mg/m², and vincristine 1.4 mg/m² on day 1, prednisolone 100 mg/day on days 1 to 5, and rituximab 600 mg on day 4. The patient showed significant level of consciousness improvement with a GCS of E4VtM6 on the second day of chemotherapy, and also showed significant improvement in his serum lactate levels the following day. His serum lactate level decreased to 1.9 mmol/L on the fourth day of chemotherapy.
He developed disseminated intravascular coagulation syndrome associated with tumor collapse immediately after completion of the chemotherapy, and therefore he remained in the ICU. His general condition gradually improved. Renal replacement therapy was resumed because he experienced a transient decreased renal function that seemed to be due to tumor lysis syndrome following chemotherapy. His renal function gradually improved and normal urination became possible. By 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 into the general ward. Lumbar puncture was performed due to suspicion of central nervous invasion by tumor cells as the cause of his impaired consciousness. However, a definitive diagnosis of central nervous system invasion could not be pathologically made. Three weeks after the first chemotherapy regimen, he was administered doxorubicin 50 mg/m\(^2\), cyclophosphamide 750 mg/m\(^2\), and vincristine 1.4 mg/m\(^2\) on day 1, and prednisolone 100 mg/day on days 1 to 5 as the second chemotherapy regimen. 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 2745 U/mL just before transferring to another hospital. His clinical condition was under control and on the seventy-seventh 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

Hyperlactatemia, which cannot be normalized even by powerful blood purification therapy, was observed in this case. In the previous hospital, the patient was treated with intermittent blood purification while simultaneously being treated with high flow continuous hemodiafiltration. Severe lactic acidosis was diagnosed as a pathological condition in this patient and was treated by powerful blood purification therapy while maintaining the acid-base balance. When lactic acidosis is associated with malignant lymphoma, as in this case, elevated lactic acid level (>5 mmol/L) and lactic acidosis are observed in 15% and 1.8% of hematological malignancies, respectively\(^1,2,3\). Among these reports, there is only one other case of lactic acidosis accompanying intravascular lymphoma. Ours is the first report in which the patient survived.

Lactic acidosis is divided into two categories, Type A and B. When hypoxemia is observed, it is Type A lactic acidosis. Type B is defined as not having clinical evidence of hypoxemia and is associated with systemic disease, such as renal or hepatic failure, and diabetes. Type A lactic acidosis occurs in association with ischemic bowel syndrome, sepsis, cardiogenic shock, and advanced dehydration. It is most frequently seen in cases of tissue hypoperfusion and 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 drugs\(^4\).

This patient required mechanic ventilation support for respiratory failure exacerbated by hypoxemia. Pneumonia, pulmonary embolism, and congestive heart failure were
suspected as the cause of respiratory failure from the clinical course at the time of tracheal intubation. However, these conditions were excluded by various culture tests, imaging results, and echocardiography. Non-cardiogenic pulmonary edema was suggested to be the main etiology of respiratory failure, because water balance management by renal replacement therapy led to improvement in the patient’s physical state. However, even after improvement in the hypoxemia, the patient showed no improvement in the acidosis. Because of this, the acidosis was considered to be Type B. Immediately after transferring to the ICU in our hospital, contrast computed tomography was performed to check for suspicious intestinal ischemia; none was found. At the initial stage of therapy in the ICU, broad spectrum antimicrobial and antifungal drugs were administered simultaneously for suspected septic shock, a suspicion that was discounted once results of various culture tests were negative.

If diseases causing lactic acidosis are divided according to the mechanism of lactic acid elevation, there are conditions that lead to an increase in lactic acid production, such as pheochromocytoma, respiratory alkalosis, and glycogenosis type 1, and there are diseases that cause a decrease in the turnover of lactic acid, such as alcohol polydipsia and liver disease. There are also diseases whose detailed mechanisms of lactic acid elevation are unknown, such as malignant tumors, acquired immunodeficiency syndrome (human immunodeficiency virus infection), and hypoglycemia.

Only one other case report has described lactic acidosis because of intravascular lymphoma; however, it did not report a detailed mechanism of lactate elevation. The
Warburg effect, a phenomenon observed as an 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, cells have increased accumulation of hypoxia inducible factor-1α. As a consequence, overexpression of glucose transporters/glycolytic enzymes and suppression of mitochondria metabolism occur, resulting in increased glucose uptake and excessive lactic acid production\(^1\). However, hypoglycemia was not observed in this case.

In cancer patients, lactic acidosis has an even worse prognosis, with a mortality rate >80\(^%\)^8. In some cases, chemotherapy cannot be performed, because the patient’s physical status is in decline and their general condition is poor. However, no patients suffering from intravascular lymphoma have improved without receiving chemotherapy, as it is the only lifesaving treatment\(^2\).\(^6\).

Regarding chemotherapy administration during renal replacement therapy, it is often difficult to determine the dosage and administration schedule of medication. Moreover, the regimen differs according to the blood purification therapy type, whether it be intermittent or continuous renal replacement therapy. Since this patient developed significant hyperlactatemia, continuous renal replacement therapy was performed before the chemotherapy and was continued even after chemotherapy. Regarding the regimen of chemotherapy to be administered with blood purification therapy, it is necessary to consider not only the patient’s age and physical status, but also the ability of the drug to be administered during dialysis, the dosage, and the timing of blood purification
therapy. Intermittent blood purification is associated with problems of toxicity accumulation and fluid retention on the days of non-dialysis. In contrast, continuous renal replacement therapy, frequently performed in ICUs, provides constant dialysis performance and management of body fluid moisture, even though dialysis efficiency and substance removal efficiency are inferior compared to intermittent blood purification. Designing 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. This patient was an ideal case for this type of renal replacement therapy.

Tumor lysis syndrome is 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 leading to multiple organ dysfunction. This syndrome requires immediate treatment, since the disintegration of tumor cells proceeds rapidly, and intracellular substances such as uric acid flowing out into the blood obstruct renal tubules, leading to renal failure. Active administration of continuous renal replacement therapy to compensate for renal dysfunction as part of early treatment for tumor lysis syndrome enables continuation of chemotherapy and eventual recovery from renal dysfunction. In this case, it was difficult to normalize the blood lactate levels using blood purification in the ICU. However, renal replacement therapy was performed for this patient prior to administration of chemotherapy, and was continued after chemotherapy for the acute renal failure that accompanied tumor
collapse. The patient's renal function gradually improved, eliminating 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 level of consciousness improved significantly through critical care management and chemotherapy, allowing the patient to survive. We should note that critical care management centered on renal replacement therapy may make it possible to receive chemotherapy in the ICU and lead to good clinical outcome.

Conflict of Interest: None. The authors declare no conflict of interest.
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Figure legends

Table 1. The patient characteristics at the ICU admission.

ICU, intensive care unit; FiO$_2$, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PaO$_2$, partial pressure of arterial oxygen; PaCO$_2$, 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

Figure 1. The patient’s clinical course after transfer to the ICU in our hospital.

Mechanical ventilation support and continuous renal replacement therapy were continued to treat respiratory failure and severe lactic acidosis, respectively. Respiratory condition and circulatory dynamics stabilized, and acidosis was improved.

Consciousness level and hyperlactatemia did not improve. Chemotherapy was started on the seventh day in the ICU. A significant improvement in the level of consciousness (Glasgow Coma Scale) was observed the day after the first day of chemotherapy. Serum
lactate levels also significantly decreased and normalized 2 days after beginning chemotherapy.

ICU, intensive care unit; MEPM, meropenem; LZD, linezolid; MCFG, micafungin;

PaO$_2$, partial pressure of arterial oxygen; FiO$_2$, fraction of inspired oxygen
Figure 1

Continuous renal replacement therapy
Mechanical ventilation

MEPM/LZD/MCFG
Doxorubicin
Cyclophosphamide
Vinca alkaloid
Roxanol

Norepinephrine (mcg/kg/min)
0.2 0.1 0.05

PAO2/FIO2 ratio
Systolic blood pressure
Heart rate
Lactate
Glasgow Coma Scale

ICU stay days
Table 1

**Respiratory physiology**

| Parameter                                      | Value |
|------------------------------------------------|-------|
| Minute ventilation (L/min)                    | 12    |
| FiO₂                                           | 0.6   |
| Driving pressure (cmH₂O)                      | 15    |
| PEEP (cmH₂O)                                  | 10    |
| PaO₂/FiO₂ ratio                               | 187   |
| pH                                             | 7.181 |
| PaCO₂ (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**

| Parameter                                      | Value     |
|------------------------------------------------|-----------|
| 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)                        | 4000      |
| Hemoglobin (g/dL)                              | 10.7      |
| Hematocrit (%)                                 | 32.5      |
| Platelets (10⁴/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