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# Severe lactic acidosis in association with CD5+ large B-cell lymphoma

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## Abstract

Lactic acidosis is classified into type A and type B. In cases of type B lactic acidosis, it is important to consider underlying lymphomas, mostly B-cell types, such as intravascular large B-cell lymphoma (IVLBCL) or diffuse large B-cell lymphoma. Cluster of differentiation (CD) 5+ large B-cell lymphoma (LBCL) is well-known for its aggressive nature. We report here two cases of CD5+ LBCL that showed severe lactic acidosis (11.2 mmol/L and 15.9 mmol/L, respectively; reference range: 0.6–1.7) with hypoglycemia. Case 1 was a 79-year-old female who presented with multiple organ failure. CD5+ IVLBCL was diagnosed through a random skin biopsy in this patient. Case 2 was a 78-year-old female with bone marrow involvement by CD5+ LBCL cells and liver failure. The patient was also diagnosed pathologically as IVLBCL by liver biopsy. Both patients were under ventilator management and high-flow continuous hemodialysis and filtration. Plasma exchange was also employed. An anti-lymphoma regimen (a 50% dose-reduced etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) was introduced on day 11 and day 2 of hospitalization for cases 1 and 2, respectively. In Case 1, lactic acidosis was normalized within day 17, and the patient survived longer than 8 weeks, while in Case 2, lactic levels did not improve until her death on day 16 of hospitalization. In conclusion, prompt recognition of type B lactic acidosis and early diagnostic biopsy are essential for improving outcomes in aggressive CD5+ IVLBCL, highlighting the need for novel therapeutic strategies.

***Keywords:*** CD5+ large B-cell lymphoma; Lactic acidosis; Intravascular large B-cell lymphoma; Random skin biopsy; Liver biopsy; Chemotherapy; Ventilator management; Continuous hemodialysis and filtration

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## 1. Background

Cluster of differentiation (CD) 5+ large B-cell lymphoma (LBCL) was classified as one of the immunohistochemical lymphoma subgroups in the 2008 World Health Organization classification.[1] It is common in elderly patients, shows a female predominance, and is characterized by advanced-stage disease at diagnosis, elevated serum lactate dehydrogenase (LDH) levels, frequent extranodal involvement (bone marrow, hepatosplenic, and central nervous system [CNS]), and a poor prognosis.[2,3] The lymphoma may develop as intravascular large B-cell lymphoma (IVLBCL)[4,5] or diffuse large B-cell lymphoma (DLBCL).[6-8]

Lactic acidosis occurs as type A (hypoxia in shock-related) or type B (malignant neoplasm-related, metformin toxicity in diabetics, etc.)[9] Type B lactic acidosis, secondary to the Warburg effect in malignant cells, is one of the clinical features associated with IVLBCL,[4,10,11] which has also been reported in other lymphomas, such as Burkitt's lymphoma and DLBCL.[8,12-15] Type B lactic acidosis differs from type A lactic acidosis,[16–18] which is caused by tissue hypoxia resulting from low tissue perfusion, typically associated with septic or cardiogenic shock. However, both types show similarly high lactate levels in the peripheral blood.

Intravascular LBCL is a rare and clinically aggressive lymphoma characterized by the proliferation of LBCL within the lumen of small-caliber blood vessels, consisting of a classical variant (Western) or a hemophagocytic variant (Asian).[19] In Japanese, CD5+ IVLBCL was noted in 38% of cases.[20] Pathological diagnosis of IVLBCL is performed with biopsies of the affected tissues or normal skin (random skin biopsy [RSB]).[21,22] On the other hand, cases of aggressive LBCL with primary bone marrow involvement include various types of lymphoma, such as IVLBCL and bone marrow-liver-spleen (BLS)-type DLBCL.[23] Among such cases, patients with hepatic failure syndrome often show portal and intra-sinusoidal infiltration of lymphoma cells in the liver, either with[4,5] or without intravascular involvement.[6,7] Pathologically, CD5+ LBCL cells show a CD5+, CD10−, CD20+, B-cell lymphoma (BCL) 2+, BCL6−, and multiple myeloma (MUM1)+ phenotype.[3] We report here two cases of CD5+ IVLBCL with severe lactic acidosis, which were treated with anti-lymphoma chemotherapy after the diagnosis.

## 2. Case presentation

### 2.1. Case 1

A 79-year-old non-diabetic female with a history of bronchial asthma was transferred to our emergency department with respiratory distress and dehydration after influenza and COVID-19 infections. The patient was conscious and afebrile with blood pressure (BP) of 127/87 mmHg, heart rate (HR) of 88/min, respiratory rate (RR) of 25/min, and peripheral capillary oxygen saturation ($SpO_2$) of 98% (room air). Imaging studies (X-rays, computed tomography [CT], and ultrasound [US]) showed that she had ascites, splenomegaly, and gallbladder wall thickening, but no pneumonia. The patient was not in an episode of asthma at the time of admission. The respiratory distress was not attributable to his asthma. Arterial blood gas analysis revealed a pH of 7.315, $HCO_3^-$ 13.4 mEq/L, base excess (BE) −11.2, and lactate 11.2 mmol/L. Other laboratory data included a white blood cell (WBC) of 4,900/μL, hemoglobin (Hb) 11.3 g/dL, and platelet count 48,000/μL. Hemostatic data showed an abnormal prothrombin time–international normalized ratio (PT-INR) of 1.58, whereas activated partial thromboplastin time (APTT) was within normal range. Her biochemical data (normal ranges shown in Table 1) revealed elevated levels of C-reactive protein (CRP; 30.3 mg/dL), aspartate aminotransferase (AST; 458 U/L), alanine aminotransferase (ALT; 342 U/L), lactate dehydrogenase (LDH; 3,381 U/L), triglyceride (163 mg/dL), total bilirubin (1.67 mg/dL), blood urea nitrogen (BUN; 26.8 mg/dL), ferritin (2,197 ng/mL), and soluble interleukin-2 receptor (IL-2R; 5,278 U/mL). Decreased levels were observed for glucose (53 mg/dL), total protein (5.6 g/dL), and albumin (2.7 g/dL). Serum creatinine rose from 1.05 mg/dL at presentation to 1.36 mg/dL on day 3, indicating progressive renal dysfunction.

After hospitalization, the patient was started on intravenous hydration and antibiotic therapy. Despite these interventions, lactate levels remained elevated for 3 days. Due to severe multi-organ failure and lactic acidosis, she was placed on a mechanical ventilator and high-flow continuous hemodialysis and filtration (CHDF). On day 3, plasma exchange (PE) was also attempted. Because the underlying cause of lactic acidosis remained unknown, an RSB[21,22] was performed on day 4 from five sites: The middle and right lower abdomen, right and left inner thighs, and the right upper arm. Unfortunately, because of the year-end and New Year holidays, the pathological diagnosis was delayed, which was confirmed on day 11. The results showed IVLBCL with CD5+, CD20+ (Figure 1), MUM1+, and Ki-67 labeling index of nearly 100%, while Epstein–Barr virus-encoded small RNA *in situ* hybridization phenotype was positive at the thigh skin but not at the abdominal and upper arm skins. Her bone marrow was hypocellular with a few hemophagocytes.

A correlation between the therapeutic measures and lactate levels during the initial 3 weeks was summarized

**Table 1. Summary of two cases of CD5⁺ LBCL with lactic acidosis**

| Clinical profile | Case 1 | Case 2 |
|---|---|---|
| Age (years)/gender | 79/F | 78/F |
| Lymphoma type | IVLBCL | IVLBCL |
| Laboratory data (references) | | |
| WBC (3300–8600/μL) | 4,900 | 5,800 |
| Hb (11.6–14.8 g/dL) | 11.8 | 10.9 |
| Platelet count (158,000–348,000/μL) | 48,000 | 95,000 |
| CRP (0.00–0.14 mg/dL) | 30.3 | 3.46 |
| LDH (124–222 U/L) | 3,381 | 2,434 |
| Total bilirubin (0.4–1.5 mg/dL) | 1.67 | 5.82 |
| Albumin (4.1–5.1 g/dL) | 2.7 | 3.2 |
| Triglyceride (30–117 mg/dL) | 163 | 323 |
| PT-INR (0.9–1.1) | 1.58 | 2.14 |
| Creatinine (0.46–0.79 mg/dL) | 1.05 (day 3, 1.36) | 2.37 |
| Glucose (73–109 mg/dL) | 53 | 69 |
| Ferritin (12–60 ng/mL) | 2,197 | 565 |
| Soluble IL-2R (122–496 U/mL) | 5,278 | 10,827 |
| Gas analysis | | |
| pH (7.35–7.45) | 7.315 | 7.161 |
| Lactate (0.6–1.7 mmol/L) | 11.2 | 15.9 |
| Management | | |
| Ventilator management (days) | >56 | 14 |
| CHDF (days) | 30 | 9 |
| Plasma exchange | Twice | Once |
| Biopsy of the involved organs | RSB (day 4) | Liver biopsy (day 2) |
| Start of DA-etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab introduction | Day 11 | Day 2 |
| Outcome | | |
| Normalized serum bilirubin (weeks) | <5 | No |
| Normalized lactate (weeks) | <3 | No |
| Normalized soluble IL-2R (weeks) | >8 | No |
| Outcome | Alive >8 weeks | Died on day 16 |

Abbreviations: CHDF: Continuous hemodialysis and filtration; CRP: C-reactive protein; Hb: Hemoglobin; IL-2R: Interleukin-2 receptor; IVLBCL: Intravascular large B-cell lymphoma; LBCL: Large B-cell lymphoma; LDH: Lactate dehydrogenase; PT-INR: Prothrombin time-international normalized ratio; RSB: Random skin biopsy; WBC: White blood cell.

in Figure 2. Initially, with PE combined with high-flow CHDF, lactate levels declined to 3.4 mmol/L. Continuation of hydration/antibiotics did not improve the condition. In

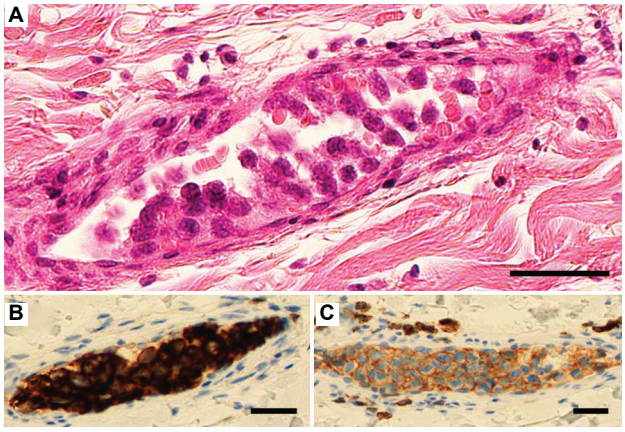


**Figure 1.** Pathology of random skin biopsy in Case 1. (A) Large blasts are noted in the intravascular space (hematoxylin and eosin stain) in the cutaneous tissue. Magnification: ×200. Scale bar indicates 50 μm. (B) Tissue stained with anti-CD20 antibody. Magnification: ×200. Scale bar indicates 50 μm. (C) Tissue stained with anti-CD5 antibody. Magnification: ×200. Scale bar indicates 50 μm. Stains of MUM1⁺, Ki-67⁺, and Epstein–Barr virus-encoded small RNA *in situ* hybridization⁻ are not shown
Abbreviation: CD: Cluster of differentiation

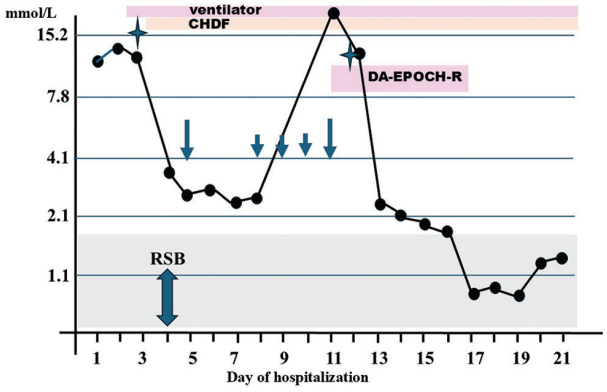


**Figure 2.** Longitudinal lactate levels during the early hospital days in Case 1 (from day 1 to day 21). The lactate unit is mmol/L. Reference ranges are shown as gray areas (0.6–1.7 mmol/L). Dose of methylprednisolone was indicated by the arrows (long arrow 1 g/dose, short arrow 60 mg/dose). A DA-etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab regimen was given on day 11. The cross mark indicates plasma exchange. Ventilator management and CHDF continued longer than 3 weeks.
Abbreviations: CHDF: Continuous hemodialysis and filtration; RSB: Random skin biopsy.

the absence of a confirmed diagnosis, methylprednisolone was administered from day 8 to day 11; this treatment was ineffective, and lactate levels rose again to 29.6 mmol/L on day 11. After the pathological diagnosis of CD5⁺ IVLBCL, the introduction of a second PE and a DA-EPOCH-R regimen (etoposide/vincristine/doxorubicin/cyclophosphamide/prednisolone, rituximab)[24] (in this case, a 50% dose-reduced regimen except for prednisolone) from day 11 to day 17 worked effectively. The dose reduction of the

50% regimen was employed considering her age and poor performance score (under ventilator management and CHDF). Eventually, severe lactic acidosis normalized on day 17 (Figure 2). Thereafter, serum bilirubin normalized within 5 weeks, whereas the serum ferritin remained high at 2,832 ng/mL and LDH levels at 570 U/L. Serum total protein and albumin levels remained low. These findings indicated persistent lymphoma activity. Although she survived for over 8 weeks of hospitalization, further chemotherapy was precluded by marked deterioration in the patient's condition.

### 2.2. Case 2

A 78-year-old female with bone marrow involvement by CD5⁺ LBCL and liver failure presented at our hospital for evaluation. The patient had a history of rheumatoid arthritis (RA) with RA-associated interstitial lung disease and had been treated with methotrexate and tocilizumab. Since patients with RA have a greater risk of developing lymphoma than the general population,[25] this patient may have had a predisposition to lymphoma development. The detection of CD5⁺ LBCL cells (13.8%), which exhibited a complex karyotype in the patient's bone marrow, was reported by the previous medical institution. Chest and abdominal CT revealed bilateral interstitial shadows in the lungs, hepatosplenomegaly, and swollen periportal lymph nodes without portal thrombus. However, neither systemic lymphadenopathy nor apparent space-occupying lesions in the liver were identified. She was afebrile, severely icteric with slightly disturbed consciousness, with BP of 118/71 mmHg, HR of 100/min, RR of 19/min, and $SpO_2$ of 97% (room air). Arterial blood gas analysis showed a pH of 7.161, $HCO_3^-$ 7.2 mmol/L, BE −19.6 mmol/L, and lactate 15.9 mmol/L. Other laboratory data included WBC 5,800/μL, Hb 10.9g/dL, platelet count 95,000/μL, PT-INR 2.14, APTT 39.7 s, serum CRP 3.46 mg/dL, AST 349 U/L, ALT 181 U/L, LDH 2,434 U/L, total protein 6.4 g/dL, albumin 3.9 g/dL, total bilirubin 5.82 mg/dL, triglyceride 323 mg/dL, soluble IL-2R 10,827 U/mL, ferritin 565 ng/mL, BUN 87.0 mg/dL, creatinine 2.37 mg/dL, uric acid 32.6 mg/dL, and blood glucose 69 mg/dL. Since the patient showed primary bone marrow involvement associated with hepatosplenomegaly, either BLS-type DLBCL or IVLBCL, which shows similar presentations, was clinically suspected.[23,26]

The patient underwent an RSB and a US-guided percutaneous needle biopsy of the liver. The RSB was performed at three sites—the chest, left thigh, and upper abdomen—and all were negative. The liver was diffusely infiltrated by large atypical lymphoblasts, which occupied the sinusoids and extended into the portal regions and hepatic cords (Figure 3), leading to a diagnosis of IVLBCL. However, the patient's complex karyotype in the bone marrow lacked 19q13 abnormalities and the 8p21 deletion, which are commonly found in IVLBCL;[20] thus, the diagnosis was particularly challenging. Immuno-histochemistry showed positivity for CD5, CD20, BCL2, BCL6, MUM1, and negativity for programmed death-ligand 1 (PD-L1), CD3, CD10, cytokeratin, and pancytokeratin (AE1/AE3). Her clinical course is summarized in Figure 4, in which ventilator management, PE, and high-flow CHDF were introduced because of severe liver dysfunction and lactic acidosis. In addition, based on the information on CD5⁺ LBCL cells in bone marrow from the previous medical institution, we initiated a 50% dose-reduced

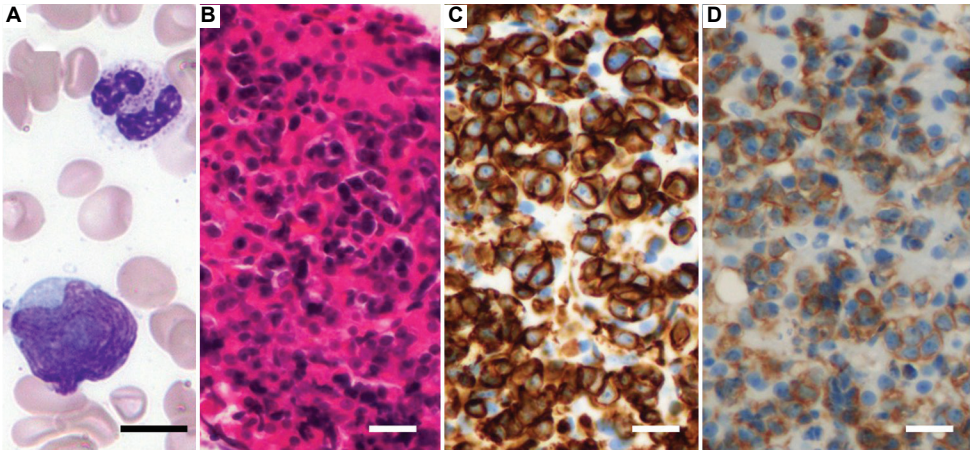


**Figure 3.** Lymphoma cells in the bone marrow smear and pathology in the liver biopsy of case 2. (A) CD5⁺ large B-cell lymphoma blasts were scattered in the bone marrow smear. Magnification: ×1000. Scale bar indicates 10 μm. (B) Diffuse infiltration of lymphoma cells in the liver (hematoxylin and eosin stain). Magnification: ×200. Scale bar indicates 50 μm. (C) Cells stained with anti-CD20 antibody. Magnification: ×200. Scale bar indicates 50 μm. (D) Cells stained with anti-CD5 antibody. Magnification: × 200. Stains of MUM1⁺, Ki-67⁺, c-Myc⁺, and Epstein–Barr virus-encoded small RNA *in situ* hybridization⁻ are not shown. Abbreviation: CD: Cluster of differentiation.

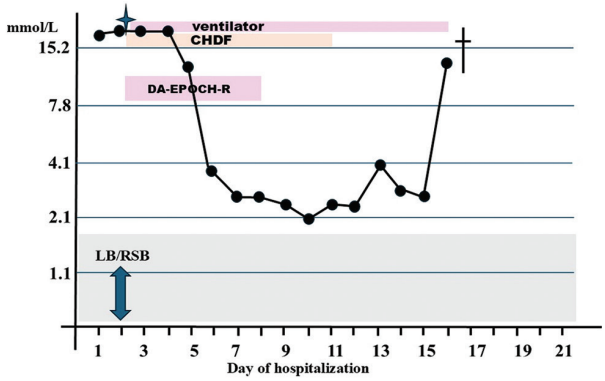


**Figure 4.** Longitudinal lactate levels during the early hospital days in Case 2 (from day 1 to day 21). The lactate unit is mmol/L. Reference ranges are shown as gray areas (0.6–1.7 mmol/L). A DA-etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab regimen was introduced on day 2 of hospitalization. The patient died on day 16 of hospitalization (indicated by the cross mark). Ventilator management and CHDF were provided for a shorter duration compared to case 1. Abbreviations: CHDF: Continuous hemodialysis and filtration; LB: Liver biopsy; RSB: Random skin biopsy.

EPOCH-R regimen, which was similar to Case 1, on day 2 of hospitalization. However, lactic acidosis, high serum LDH, and soluble IL-2R persisted, and renal dysfunction deteriorated within 3 weeks. The patient succumbed on day 16 of hospitalization.

Laboratory data for the two cases are comparatively summarized in Table 1.

## 3. Discussion

Both patients required ventilator management, high-flow CHDF, and PE, likely due to hypercytokinemia related to IVLBCL, causing respiratory, hepatic, and renal dysfunction.[19-23,26-30] Aggressive CD5⁺ LBCL is well recognized with a poor outcome.[2,3] Previously, the fatal outcome in cases of CD5⁺ IVLBCL presented without[4] or with lactic acidosis[5] was reported. Similarly, we report here two cases of CD5⁺ IVLBCL associated with severe lactic acidosis and liver dysfunction. It appears that the prognosis of aggressive lymphoma worsens when accompanied by lactic acidosis. In Case 1, to determine the cause of type B lactic acidosis, we performed an RSB on day 4; however, the IVLBCL diagnosis was delayed because pathology services were unavailable during national holidays. Accordingly, we administered methylprednisolone for 4 days, which was not effective. Previously, the failure of empiric steroid treatment was described in a case of IVLBCL.[10] Thus, after the definite diagnosis, anti-lymphoma chemotherapy (a 50% dose-reduced EPOCH-R regimen) was administered, considering her age and poor performance score. This regimen, CHDF, and PE effectively normalized lactate levels, as shown in Figure 2. In Case 2, which represents a more advanced stage of IVLBCL with initial CD5⁺ LBCL involvement of the bone marrow progressing to liver failure, severe lactic acidosis was also observed. In this case, we initiated anti-lymphoma treatment shortly after hospitalization without waiting for confirmation from the liver biopsy pathology. Nevertheless, resolution of hepatic dysfunction and lactic acidosis was delayed, and the patient succumbed.

Lactic acidosis is defined as a condition with a pH below 7.35 and blood lactic acid levels > 5 mmol/L.[14,17] In lymphoma-related type B lactic acidosis, Duriseti *et al.*[15] summarized that the initial mean serum lactate level was 12.4 mmol/L (range: 2.4–24.0 mmol/L) with a peak mean value of 16.8 mmol/L (range: 4.9–28.5 mmol/L). The lactate levels in our cases were compatible with their report. Type B lactic acidosis occurs without tissue hypoxia due to increased aerobic glycolysis and excess lactic acid formation in the tumor (known as the Warburg effect), which has been described in hematological malignancies and rarely in solid malignancies. This type B lactic acidosis, one of the oncology emergencies, could effectively be treated by the prompt initiation of chemotherapy. However, treating type B lactic acidosis in CD5⁺ IVLBCL cases remains challenging. On the other hand, in the literature of type A lactic acidosis, 239 surgical patients with severe hyperlactatemia (>10 mmol/L) treated in the surgical intensive care unit were reported, in which the peak lactate level was significantly higher in the non-survivor group (17.8 ± 5.8 mmol/L) than the survivor group (13.9 ± 4.4 mmol/L, $p$=0.001).[18] These findings indicate that lactic acid levels cannot differentiate between type A and type B lactic acidosis in terms of severity.

Intravascular LBCL with or without CD5 expression has not been reported to involve various organs, such as skin, lungs, bone marrow, spleen, liver, kidneys, testis, muscles, endocrine organs (mostly pituitary, thyroid, and adrenal glands), and the CNS.[19,27] Among Japanese, CD5⁺ IVLBCL was noted in 38% of cases.[20] As for cases with various organ damage symptoms due to IVLBCL, a 62-year-old man with asthma presented with a 1-month history of wheezing and exertional dyspnea due to the pulmonary IVLBCL.[28] In addition, a case of CD5⁺ IVLBCL with renal dysfunction was diagnosed using a renal biopsy.[29] On the other hand, hepatic LBCL, similar to Case 2, may consist of IVLBCL[10,11,30] or DLBCL.[3,6,7] In one hepatic IVLBCL case,[10] a liver biopsy showed extensive intra-sinusoidal lymphoma involvement with complete obliteration of all portal tracts by the lymphoma infiltrate. Another hepatic IVLBCL case[11] showed nodular and sinusoidal parenchymatous invasion by large lymphomatous cells. The hepatic pathology in

Case 2 was diagnosed as IVLBCL with the extra-vascular infiltration of lymphoma cells beyond the portal and sinusoidal regions. Thus, the two CD5+ IVLBCL cases described here might have had extensive and rapid growth of lymphoma cells in multiple organs, which were thought to be responsible for severe lactic acidosis.

In IVLBCL cases requiring RSB, a biopsy from normal-appearing skin can be valuable for IVLBCL diagnosis. MacGillivary *et al.*[22] recommended RSB for patients with a fever of unknown origin, anemia, thrombocytopenia, and high serum LDH/ferritin, but with no lymphadenopathy. Three to four RSBs from the thigh, abdomen, and posterior upper arm need to be performed with either incisional or telescoping punch biopsies. In RSB procedures, Enzan *et al.*[31] recommended taking specimens from normal-appearing and any other skin lesions, because cutaneous lesions may reflect micro IVLBCL.

Treatment of patients with type B lactic acidosis primarily focuses on treating the primary disease, such as anti-lymphoma chemotherapy, rather than lactic acid correction and fluid rehydration treatment alone.[15,32] Resolution of lactic acidosis was reported to occur as early as 15 h and up to 3 days after starting chemotherapy. Malignancy-induced lactic acidosis carries a poor prognosis with a mortality rate of >90%.[32] A previous study showed that only 2/28 patients with malignant lymphoma achieved a complete remission (CR), whereas >75% died within 1 month.[33] More recently, a review by Duriseti *et al.*[15] showed that of 37 cases of type B lactic acidosis, 32 received chemotherapy, whereas five did not. In the former group, 12 attained a CR of lymphoma, with six of them showing a rapid decline of lactate levels. For the remaining 20 patients who did not achieve CR, four of them survived but with delayed improvement of lactic acidosis. In contrast, all five patients who did not receive chemotherapy died.

Liver failure, as observed in Case 2 of our study, has also been reported in a 45-year-old male with CD5+ LBCL described by Sato *et al.*,[6] who was successfully treated with PE, bilirubin absorption, CHDF, and the R-CHOP regimen. On the other hand, Miyazaki *et al.*[34] proposed a DA-EPOCH-R regimen (rather than R-CHOP) with high-dose methotrexate for CNS prophylaxis because of the high risk of CNS lesions. In our two elderly patients with severe lactic acidosis, treatment with a 50% dose-reduced EPOCH-R regimen might have been initiated too late, given the advanced stage of CD5+ IVLBCL. High-dose methotrexate for CNS prophylaxis could not be administered in either case, and the outcomes of both cases were poor. Regarding the poor outcome in CD5+ LBCL, PD-L1 expression was previously shown in BLS-type DLBCL[26] and IVLBCL.[35] The PD-L1 in our Case 2 was tested, but was negative. Incorporating nivolumab or pembrolizumab in future regimens for PD-L1-positive IVLBCL or BLS-type DLBCL may improve the outcome.

## 4. Conclusion

When type B lactic acidosis is noted in patients, a rapid search for underlying diseases, such as aggressive lymphoma (CD5+ IVLBCL), is required. For this purpose, a timely biopsy must be performed for random skin or organs involved. We conclude that the prognosis of aggressive CD5+ LBCL worsens when accompanied by severe lactic acidosis. Accordingly, innovative therapeutic procedures must be investigated to efficiently manage lactic acidosis and attain a complete response to lymphoma.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

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*Writing–review & editing:* All authors

## Ethics approval and consent to participate

The work was conducted in accordance with the Declaration of Helsinki as revised in 2013. This case report is approved by the institutional review board (Uji-Tokushukai Medical Center Ethics Committee; IRB approval No. 2025-12). Written informed consents were obtained from the patients' families.

## Consent for publication

All participants gave their permission to publish their data.

## Availability of data

Data are available on request from the authors.

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