Acute liver failure (ALF) is a relatively rare presentation of non-Hodgkin lymphoma, often found only during postmortem examination in patients. We treated a 33-year-old woman with prominent jaundice who was diagnosed with diffuse large B-cell lymphoma presenting as ALF. We could not perform liver biopsy during the critical phase because of coagulopathy, but gastric biopsy showed the infiltration of lymphoma cells. The patient was successfully treated with rituximab and chemotherapy and she survived. Malignant lymphoma should be considered in the differential diagnosis of patients who show liver dysfunction, and biopsy should be performed.

**2. Case report**

A 33-year-old Japanese woman without any medical history presented to our emergency department with upper abdominal pain, progressive jaundice, and skin rash on her face and trunk since 3 weeks. She was fully conscious and oriented. Physical examination did not reveal asterixis, hepatosplenomegaly, or lymphadenopathy. She had no history of blood transfusion, gastrointestinal bleeding, any surgical procedures, or hospitalization, nor any history of alcohol, substance abuse, or high-risk sexual behavior. Her family history was also not remarkable for hepatic disease or malignancy. Laboratory results, shown in Table 1, indicated severe hepatic damage with impaired synthetic function. The patient was diagnosed with ALF and underwent additional imaging studies to clarify the underlying cause.

Ultrasonography of the right-upper quadrant revealed an atrophied ‘potato liver’ with massive ascites. Contrast-enhanced computed tomography (CT) showed significant prominent atrophy of the liver with a mixed density area, suggesting fatty infiltration or hyperplasia and splenomegaly (Figure 1(a)). CT also revealed a dilated paraumbilical vein, indicating collateral circulation, and lymphadenopathy involving the peri-portal vein (Figure 1(b)). There was no sign of thrombosis or tumor embolus into the portal and hepatic veins, but an enlarged left cervical lymph node and slightly thickened gastric wall were observed.
The underlying cause of ALF was unknown. The patient started treatment with vitamin K and multivitamin infusion. However, on the 2nd day of hospitalization, the patient developed asterixis and deteriorated prothrombin time, and underwent steroid pulse therapy, plasmapheresis, and hemodiafiltration. Liver transplantation was considered a treatment option. As we believed that the thickened gastric wall indicated the possible presence of tumors, esophagogastroduodenoscopy was performed, which revealed depressed lesions on the gastric fundus (Figure 2(a,b)). Biopsies were taken from the lesions in the stomach, but not from the liver, because of persistent coagulopathy. Despite intensive care, encephalopathy progressed, and on the 4th day, the patient became unconscious. Brain CT revealed cerebral edema. In addition to the cerebral involvement, pulmonary vascular permeability deteriorated, indicating heart failure, probably because of the increased volume of circulating plasma.

On the 6th day of hospitalization, biopsy results from the gastric fundus revealed infiltration of large lymphocytes (Figure 3). Immunohistochemical analysis revealed positivity for cluster of differentiation (CD) 20, and many lymphocytes showed positivity for mind-bomb-1. The biopsies were negative for CD10 and CD5 and positive for B-cell lymphoma (BCL)-2, BCL-6, and multiple myeloma oncogene-1. These findings were consistent with non-germinal center B-cell-like DLBCL. The lesion was a stage IVA tumor, and the International Prognostic Index was 4. Although we could not perform liver biopsy, we speculated that the ALF was caused by the malignant lymphoma, diagnosed from the gastric sample. Peripheral blood showed slightly increased soluble interleukin-2 receptor (361 U/mL).

As chemotherapy was not performed because of multiorgan involvement, only prednisolone infusion (100 mg/day) was administered; the patient was subsequently referred to the Hematology and Oncology Department for further evaluation and management.

The patient gradually regained consciousness after continuous 100 mg/day prednisolone infusion, and her laboratory data improved. Plasmapheresis and hemodiafiltration were also stopped as a therapeutic response was observed. On the 13th day of hospitalization, 500 mg cyclophosphamide was administered with 500 mg rituximab infusion. Subsequently, she received 3 cycles of R-CP (rituximab, cyclophosphamide, and prednisolone) treatment because vincristine and doxorubicin were contraindicated owing to multi-organ failure, especially liver failure. The patient showed significant improvement, and an additional 5 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) were administered, followed by another 3 cycles of CHOP. The patient

| Table 1. Laboratory data on admission. |
|---------------------------------------|
| **Complete blood count**              |
| Hemoglobin                            | 14.3 g/dL |
| White blood cells                     | 8,490/μL |
| Platelets                             | 174,000/μL |
| **Coagulation**                       |
| PT-INR                                | 1.93     |
| **Biochemistry**                      |
| Aspartate aminotransferase            | 1249 U/L |
| Alanine aminotransferase              | 969 U/L  |
| Albumin                               | 3.0 g/dL |
| Urea nitrogen                         | 4 mg/dL  |
| Creatinine                            | 0.41 mg/dL |
| Total bilirubin                       | 25.3 mg/dL |
| Direct bilirubin                      | 16.3 mg/dL |
| Ammonia                               | 205 μmol/L |
| Serum α-fetoprotein                   | 105.3 ng/mL |
| **PIVKA-2**                           | 47 mAU/mL |
| **Serology**                          |
| Cytomegalovirus                       | IgG 8.3 |
| Epstein-Barr virus anti-VCA           | IgG 9.9 |
| Anti-EA                               | IgG 0.7 |
| Anti-EBNA                             | IgG 2.8 |
| Anti-herpes simplex virus             | IgG 44.3 |
|                                      | IgM 0.52 |
| Anti-varicella zoster                 | IgG 13.4 |
| Anti-hepatitis A                      | IgM <0.40 |
| Hepatitis surface antigen             | (-)     |
| Anti-hepatitis B core                 | IgM (-) |
| Anti-hepatitis C virus antibodies      | (-)     |
| Hepatitis C RNA                       | (-)     |
| Antinuclear antibody                  | (-)     |
| Anti-mitochondrial antibody           | (-)     |
| PIVKA-2: Protein induced by vitamin K absence or antagonist-II | (-) |
| PT-INR: Prothrombin time-international normalized ratio | (-) |

Figure 1. Abdominal contrast-enhanced computed tomography (CT) findings: Contrast-enhanced CT showed atrophy of the liver with a mixed density area, which is likely fatty infiltration or hyperplasia and splenomegaly (a). CT showing a dilated paraumbilical vein with collateral circulation (arrowheads) and lymphadenopathy involving the peri-portal vein (arrows) (b).
received treatment as an outpatient from the second course of R-CHOP treatment because her general condition had improved.

Liver biopsy performed on day 50 of chemotherapy showed obsolete necrosis of the hepatocytes and collagenized parenchyma without malignant cells (Figure 4).

Ten months after the initial diagnosis, positron emission tomography-CT showed a complete response. The laboratory data showed in Table 2, indicated all markers, including liver enzymes, were within normal limits.

3. Discussion

From an epidemiological perspective, the most common causal factors of ALF include viral infection, medications, drug use, toxins, metabolic disorders, and vascular disorders such as hepatic vein thrombosis. Invasion of tumors can also cause ALF, although no remarkable characteristics were observed on imaging in this case. Hepatic infiltration by hematological malignancies is observed in 15–22% of cases [8], and it can be the underlying etiology of ALF. However, hepatic dysfunction caused by hematological malignancies usually occurs late in the course of the disease, and liver involvement as the predominant primary presentation is relatively rare [9,10]. Hence, it is crucial to identify DLBCL as the underlying cause of ALF at the earliest possible, as early intervention with chemotherapy could potentially improve the patient’s outcome [2,11]. However, proving the hepatic involvement of DLBCL is difficult if liver dysfunction is the primary presentation. Hence, lymphoma should be suspected in patients who present with ALF, hepatomegaly, lactic acidosis, and/or a markedly elevated lactate dehydrogenase even in the absence of lymphadenopathy [2].
Biopsies are often contraindicated because of coagulopathy. In this case, liver biopsy was impossible even in the admission phase, but the gastric biopsy allowed us to identify the underlying cause. One case series showed no increase in mortality due to liver biopsy when accompanied by the administration of fresh frozen plasma and platelet transfusion [12]. Some case reports highlight the benefits of transjugular liver biopsy for evaluating the degree of hepatocyte necrosis and thus reaching a diagnosis [2,8]. This maneuver is often technically impossible in a city hospital such as ours due to lack of devices and experience, so we did not consider this option. However, if this technical problem would have been resolved, we would have used this maneuver to obtain the correct diagnosis. We were unable to identify lymphoma cell infiltration via liver biopsy on day 50. Although this was an expected result, it can be a limitation of our analysis. However, given the consistency in findings indicative of ALF and the pathological findings from gastric biopsy, we speculated that the cause of ALF was the tumor in the stomach.

In this case, CT showed thickening of the gastric fundus, for which esophagastroduodenoscopy was performed. CT scans of patients with ALF often show hepatomegaly, ascites in the abdomen, and hepatic vein occlusion [13]. However, a massively necrotic liver may appear as a nodular necrotic pattern due to parenchymal collapse of the tissue [14], which can account for our CT results.

Accurate diagnosis of lymphoma-induced ALF and prompt introduction of chemotherapy are crucial. However, the appropriate chemotherapeutic regimen for DLBCL primarily presenting as ALF remains uncertain. Care should be taken while using drugs that are metabolized by the liver. One patient was successfully treated with dose reduction of cyclophosphamide and vincristine during liver failure [8] and another was treated with three cycles of cyclophosphamide, vincristine, and doxorubicin, followed by ifosfamide, mesna, etoposide, cytosine arabinoside, and methotrexate with leucovorin rescue [2]. We gradually started chemotherapy after omitting vincristine and doxorubicin at the start of chemotherapy, owing to the patient’s liver failure. This may be a suitable treatment option for DLBCL with ALF.

Our case demonstrates that lymphoma of the liver should be considered in the differential diagnosis of ALF, even if there is no clear evidence of extrahepatic malignancy.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Patient consent**

Patient consent was obtained for publication and that the procedures followed were in accordance with the Declaration of Helsinki.

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**Table 2.** Laboratory data 10 months after the diagnosis.

| Complete blood count |  |
|----------------------|--|
| Hemoglobin           | 11.9 g/dL |
| White blood cells    | 3,180/μL  |
| Platelets            | 75,000/μL |

| Biochemistry          |  |
|-----------------------|--|
| Aspartate aminotransferase | 36 U/L  |
| Alanine aminotransferase  | 38 U/L  |
| Albumin               | 3.9 g/dL |
| Urea nitrogen         | 12 mg/dL |
| Creatinine            | 0.59 mg/dL |
| Total bilirubin       | 0.9 mg/dL |

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**Figure 4.** Histology of the liver.

Histology of the liver biopsy taken on day 50 of chemotherapy showing necrosis of the hepatocytes and collagenized parenchyma with no malignant cells (hematoxylin-eosin staining; H&E).
References

[1] Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the study of liver diseases position paper on acute liver failure 2011. Hepatology. 2012;55(3):965–967.

[2] Thompson DR, Faust TW, Stone MJ, et al. Hepatic failure as the presenting manifestation of malignant lymphoma. Clin Lymphoma. 2011;2(2):123–128.

[3] Li Y, Wang Y, Wang Z, et al. Racial differences in three major NHL subtypes: descriptive epidemiology. Cancer Epidemiol. 2015;39(1):8–13.

[4] The Non-Hodgkin’s Lymphoma Classification Project. A clinical evaluation of the international lymphoma study group classification of non-Hodgkin’s lymphoma. Blood. 1997;89(11):3909–3918.

[5] Møller MB, Pedersen NT, Christensen BE. Diffuse large B-cell lymphoma: clinical implications of extranodal versus nodal presentation – a population-based study of 1575 cases. Br J Haematol. 2004;124(2):151–159.

[6] Shimizu Y. Liver in systemic disease. World J Gastroenterol. 2008;14(26):4111–4119.

[7] Taylor DF, Cho RS, Hall J, et al. Hepatic dysfunction as presenting manifestation of Hodgkin’s lymphoma. J Gastroenterol Compl. 2016;1(1):103.

[8] Morali GA, Rozenmann E, Ashkenazi J, et al. Acute liver failure as the sole manifestation of relapsing non-Hodgkin’s lymphoma. Eur J Gastroenterol Hepatol. 2001;13(10):1241–1243.

[9] Chim CS, Choy C, Ooi CG, et al. Hodgkin’s disease with primary manifestation in the liver. Leuk Lymphoma. 2000;37(5–6):629–632.

[10] López LR, Díaz FL, Pérez BS, et al. Acute liver failure caused by primary non-Hodgkin’s lymphoma of the liver. Transplant Proc. 2016;48(9):3000–3002.

[11] Karmacharya P, Bhandari N, Aryal MR, et al. Before it crumbles: fulminant hepatic failure secondary to Hodgkin’s lymphoma. J Community Hosp Intern Med Perspect. 2014;4(5):25821.

[12] Rowbotham D, Wendon J, Williams J. Acute liver failure secondary to hepatic infiltration a single centre experience of 18 cases. Gut. 1998;42(4):576–580.

[13] Shakil AO, Jones BC, Lee RG, et al. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci. 2000;45(2):334–339.

[14] Poff JA, Coakley FV, Qayyum A, et al. Frequency and histopathologic basis of hepatic surface nodularity in patients with fulminant hepatic failure. Radiology. 2008;249(2):518–523.