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CASE REPORT

Diffuse large B cell lymphoma primarily presenting as acute liver failure in a surviving patient

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ABSTRACT

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.

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1. Introduction

Acute liver failure (ALF) refers to severe acute liver injury with encephalopathy and impaired synthetic function, such as an international normalized ratio ≥AL5, without underlying cirrhosis or preexisting liver disease [1]. Quickly determining the cause of ALF and promptly initiating chemotherapy are crucial, as rapid treatment of the underlying disease may prevent the need for liver transplantation and decrease mortality [2].

Diffuse large B cell lymphoma (DLBCL) is the most common histological type of non-Hodgkin lymphoma (NHL), accounting for about 30% of NHL cases [3,4]. The acute form of DLBCL is characterized by lymph node enlargement, night sweats, and fever, and it is normally found in the lymph nodes of the neck or abdomen but may present as a large mass anywhere in the body. NHL arises in extranodal tissues in up to 40% of cases [5]. Hepatic dysfunction occurs in 16–43% of NHL cases [6]; the pathogenesis is mostly secondary direct infiltration by the lymphoma cells, but it can present as paraneoplastic syndrome. Moreover, hepatic dysfunction is typically observed in the advanced stages, not as the primary presentation [7].

We herein report a young woman with DLBCL presenting with ALF who was successfully treated. This is an uncommon presentation of this hematological malignancy and we believe that this information will help in early diagnoses and improve patient survival.

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.

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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		25.5 mg/dL
Direct bilirubin		16.3 mg/dL
Ammonia		205 μmol/L
Serum α-fetoprotein		105.5 ng/mL
PIVKA-2		47 mAU/mL
Serology		
Cytomegalovirus	IgG	8.3
	IgM	0.53
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 B 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

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

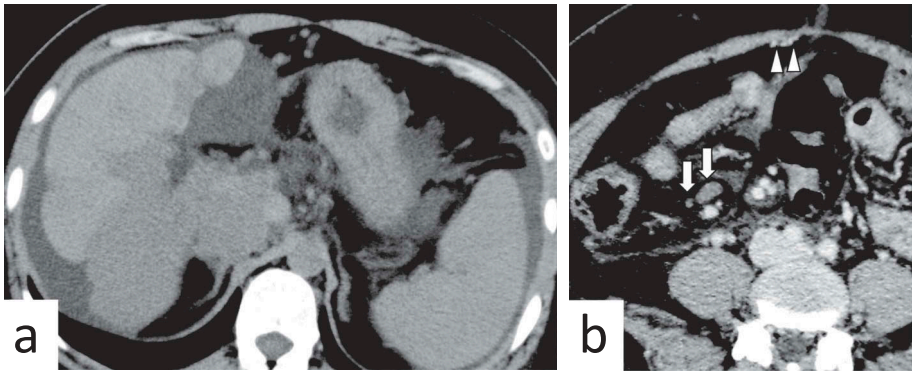

Figure 1. Abdominal contrast-enhanced computed tomography (CT) findings: Contrast-enhanced CT showed atrophy of the liver with a mixed density area, which is likely fatty infiltration or hyperplasia and splenomegaly (a). CT showing a dilated paraumbilical vein with collateral circulation (arrowheads) and lymphadenopathy involving the peri-portal vein (arrows) (b).

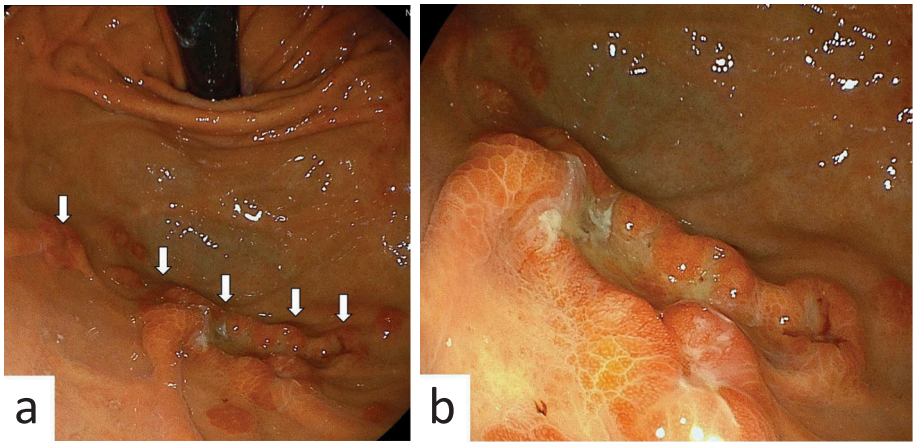

Figure 2. Esophagogastroduodenoscopy findings of the stomach.

Esophagogastroduodenoscopy revealed ulcerative lesions on the gastric fundus (arrows) (a). The auriculate ulcerative mound showed good extension in the air supply (b).

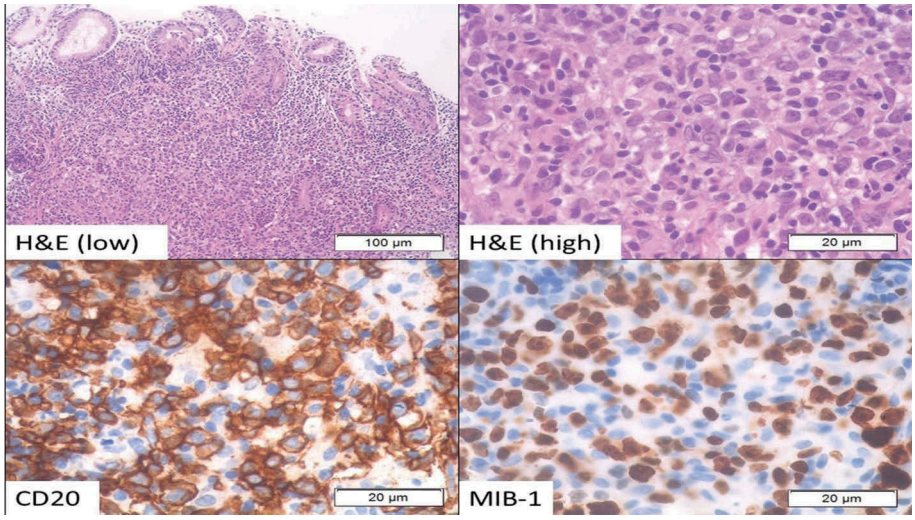

Figure 3. Histology of the stomach.

Histology of the gastric fundus showing distortion of hepatic parenchyma that was diffusely infiltrated by large lymphocytes (hematoxylin-eosin staining; H&E). Immunostaining showed numerous large cells positive for CD20 and MIB-1.

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].

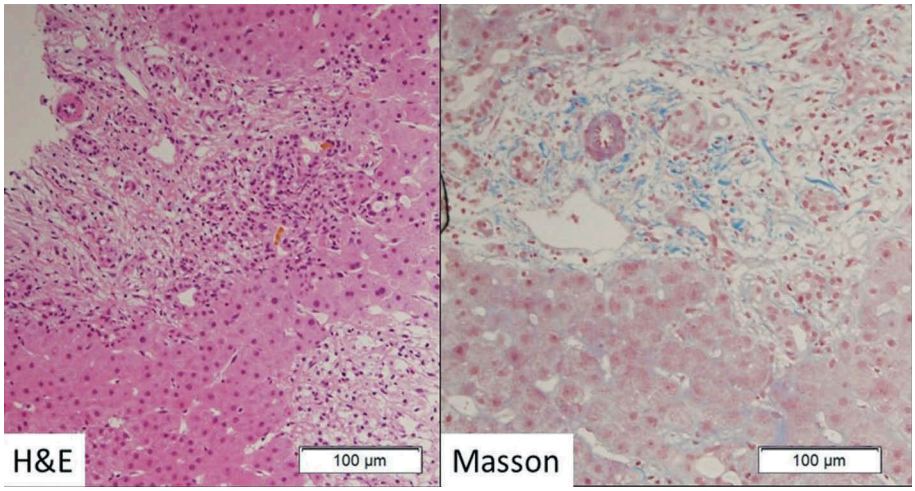

Figure 4. Histology of the liver.

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).

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

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 esophagogastroduodenoscopy 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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