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CASE REPORT

A case of intravascular lymphoma diagnosed in an explanted liver after liver transplantation

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Summary

Intravascular lymphoma (IVL) is a rare form of B-cell lymphoma. We encountered a rare case of IVL diagnosed in an explanted liver. A 49-year-old man visited a clinic with high fever. Because of elevated liver function, he was diagnosed with acute liver failure. Deceased donor liver transplantation (LT) was performed 16 days after admission. The post-transplantation course was uneventful until IVL was reported in the explanted liver on postoperative day (POD) 21. Rituximab was administered on POD 27, and rituximab–cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (R-CHOP) treatment administered on POD 38. The R-CHOP treatment was repeated for eight cycles, and the patient remains free of recurrence 1 year post-transplantation. Although systemic lymphoma is a contraindication to transplantation, our experience indicates that IVL can be successfully treated by the administration of prompt chemotherapy after LT for fulminant hepatitis.

Introduction

Intravascular lymphoma (IVL) is a rare form of systemic extranodal non-Hodgkin's lymphoma and is characterized by the proliferation of large B-lymphoma cells within the lumen of small blood vessels [1]. Generally, the clinical course of IVL is rapidly progressive and ultimately fatal [1]. Approximately 50% of cases are diagnosed postmortem with IVL [2,3].

Here, we report a case of IVL diagnosed in an explanted liver for the treatment of fulminant hepatitis. Because lymphoma infiltration was not detected in the hepatic parenchyma, the comorbid occurrence of fulminant hepatitis and IVL was assumed to be coincidental. The patient received eight cycles of chemotherapy after he was diagnosed with IVL, and he remains free of recurrence 1 year post-transplantation.

Although systemic lymphoma is a contraindication to liver transplantation (LT) because of the risk of recurrence [4,5], there may be some exceptions. Although ongoing vigilance for infectious complications and recurrence is mandatory, he may have survived because of prompt chemotherapy after IVL diagnosis following LT.

Case report

A healthy 49-year-old man developed symptoms of cough, lymphadenopathy of submandibular lymph nodes and lower leg edema. He was diagnosed with idiopathic thrombocytopenic purpura (ITP) 1 year before he developed these symptoms and was regularly monitored without medication. Six days later, he developed high fever. Eleven days later, he visited a clinic and was diagnosed with acute upper respiratory inflammation; he was treated with a cold medicine. However, he developed vertigo and started vomiting after receiving the medication. The medication was stopped because of these symptoms. Sixteen days later, he experienced epigastric pain and visited the same clinic. Laboratory tests revealed an elevated aspartate aminotransferase level of 2732 IU/l and alanine aminotransferase level of 1987 IU/l. He was referred to our hospital 18 days later with a diagnosis of acute liver failure. Vital signs on admission were blood pressure of 124/70 mmHg, heart rate of 84/min and body temperature of 36.4 °C. Laboratory data on admission are summarized in Table 1. Based on the diagnosis of acute liver failure, plasma exchange was performed. On day 20, he developed encephalopathy with a severity of grade II as per the proposal of the Inuyama Symposium, 1972 [6]. The patient's enhanced abdominal computed tomography (CT) on day 18 (Fig. 1a) and day 20 (Fig. 1b) revealed rapid progressive liver atrophy. His encephalopathy deteriorated to grade IV on day 21 and to grade V on day 22. Brain CT on day 22 did not show any edematous change, and the patient's electroencephalography results revealed cortical damage due to metabolic liver failure. His encephalopathy improved to grade IV on day 24, and he was listed for LT. On day 29, an abdominal imaging test and brain CT revealed a highly contracted liver (Fig. 2a) and no edematous change of the brain (Fig. 2b). On day 30, he received LT. The transplantation was completed in 14 h and 30 min; blood loss volume was 6830 ml, cold ischemia time was 469 min, and warm ischemia time was 49 min. Native liver volume was 690 g and graft volume was 1430 g. Splenectomy was also performed as a treatment for ITP. Subsequent immunosuppressive therapy consisted of tacrolimus and low-dose prednisone. On postoperative day (POD) 3, he was extubated, and on POD 6, he had completely regained consciousness.

The postoperative course was uneventful. On POD 21, a histological report was obtained from the explanted organs. In the vessels of the liver affected by hepatic hemangioma (Fig. 3a), atypical lymphocyte proliferation was observed (Fig. 3b–d). These were positive for CD20 and Ki67 and negative for CD3, CD5 and CD10. Atypical lymphocytes were observed among the vessels of the gallbladder (Fig. 4a and b), which were CD20 positive (Fig. 4c), and also among the splenic hilar lymph nodes (Fig. 4d–f). From the typical vesicular infiltration pattern observed, the patient was diagnosed with IVL. On POD 25, a liver biopsy was performed, and moderate acute cellular rejection was detected (Fig. 5a-d). Simultaneously, CD20-positive atypical lymphoid cell aggregation and IVL infiltration to the transplanted liver were also noted (Fig. 5e). A diagnostic bone marrow biopsy was performed on POD 26. The nucleated cell count was $1.1 \times 10^4/\mu l$, and the megakaryocyte count was 8/μl. The myeloid erythroid ratio was 2.8%, consisting of erythroblasts (20.4%), neutrophils (55.6%), lymphocytes (12.6%) and monocytes (5.4%). Pathologically, a diagnosis of normoblastic marrow with slight myelofibrosis and lymphocytes was made. On POD 27, rituximab was administered. On POD 38, a rituximab–cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (R-CHOP) treatment was administered. The R-CHOP treatment was repeated for eight cycles. One year after LT, the patient remains free of recurrence.

Discussion

We described a case of IVL diagnosed in an explanted liver. The recipient was successfully treated with chemotherapy and remains free of recurrence 1 year later. Our study presents two novel findings: first, the diagnosis of IVL is extremely difficult when it coincidentally coexists with fulminant hepatitis, and second, LT prior to chemotherapy may be a viable treatment option in such cases.

Intravascular lymphoma is a rapidly progressive and often disseminated tumor and is characterized by selective growth of lymphoma cells only in the lumina of the small vessels of various organs[1,7,8]. Classical IVL symptoms are neurological and include sensory and motor deficits, palsy, altered consciousness and seizures associated with central nervous system involvement [8]. Furthermore, an Asian variant associated with hemophagocytic syndrome has also been reported by a Japanese group [7]. In our case, the patient presented with marked deterioration of consciousness, which could be explained by coexisting fulminant hepatitis. Bone marrow and peripheral blood investigations were also performed, which did not show any infiltration. Of the laboratory data, the levels of lactate dehydrogenase (LDH) and interleukin (IL)-2, which are associated with tumor burden, were high. However, the increase in the levels of serum LDH and IL-2 could have also been caused by acute hepatitis [9]. Abdominal CT showed marked atrophy of the liver. All these objective data could be explained by fulminant hepatitis. Retrospectively, additional examinations for the preoperative diagnosis of IVL in this case could have included ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F –FDG-PET)[10] and liver biopsy. ^{18}F –FDG-PET examination was not carried out due to the patient's clinical instability for

Table 1. Laboratory data on admission.

WBC	10 100/mm^3	Amylase	48 U/l
RBC	372 × 10^4/mm^3	BUN	24 mg/dl
Hb	11.3 g/dl	Creatinine	1.17 mg/dl
Hct	36.7%	UA	4.6 mg/dl
PLT	2.4 × 10^4/mm^3	TP	4.2 g/dl
Metamyelocyte	2.0%	Alb	2.1 g/dl
Stab cell	5.0%	Ferritin	16 793 ng/ml
Segmented cell	76.0%	Procalcitonin	1.00 ng/ml
Monocyte	10.0%	IgM-HA	<0.4 S/CO
Lymphocyte	7.0%	HBsAg	0.03 IU/ml
PT%	<15%	HBcAb	0.10 S/CO
PT-INR	4.84	IgM-HBc	0.10 COI
FDP	8.6 μg/dl	HBV-DNA	<2.06 LC/ml
AT-III	20%	HCV-Ab	0.07 S/CO
D-Dimer	3.0 μg/ml	HCV-RNA	–
NH_3	168	IgA-HEV	–
AST	2422 U/l	CMV-IgM	0.50
ALT	2025 U/l	EBNA	0.8
r-GTP	51 U/l	VCA-IgG	2.4
ALP	787 U/l	ANA	<40
LAP	98 U/l	AMA-M2	<1.5
LDH	1236 U/l	AFP	2 ng/ml
CPK	137 U/l	IL2-R	16 100 U/ml
ChE	66 U/l	HGF	5.30 ng/ml

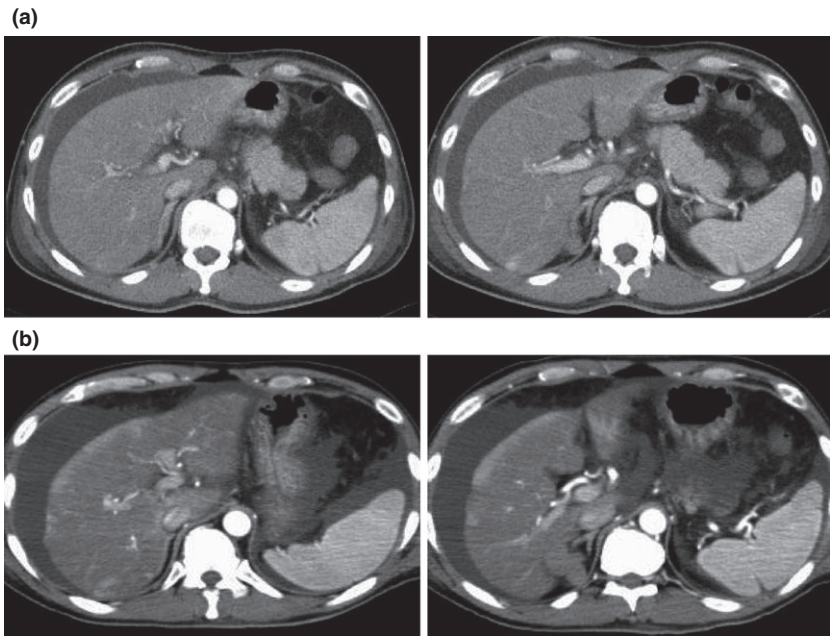

Figure 1 Abdominal enhanced computed tomography of the patient, (a) on admission and (b) 2 days after admission.

transport. In addition, because we did not suspect the coexistence of IVL, PET was considered as the last examination to be performed for differential diagnosis. The other diagnostic approach of liver biopsy, decision is made not to perform liver biopsy due to coagulopathy. Moreover, the potential efficacy of a liver biopsy in this case was questionable because IVL revealed no hepatic involvement.

Literature contains sporadic reports of acute liver failure from Hodgkin's and non-Hodgkin's lymphoma dating from 1953 [11,12]. To date, there is no report of IVL causing

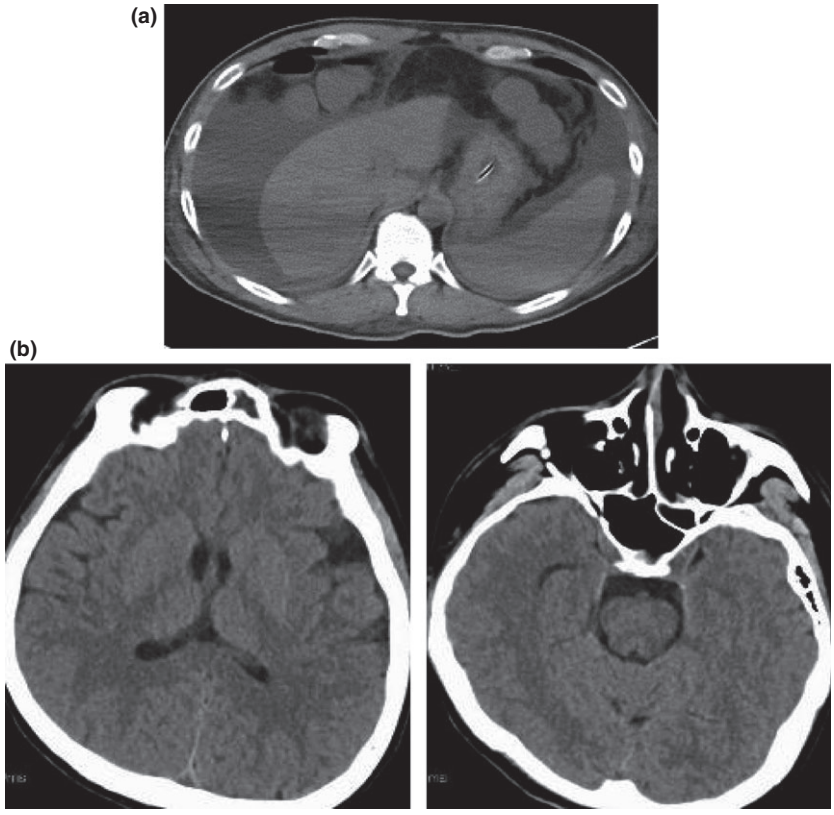

Figure 2 (a) Abdominal computed tomography of the patient on day 11 before deceased donor liver transplantation. (b) Head computed tomography on the same day.

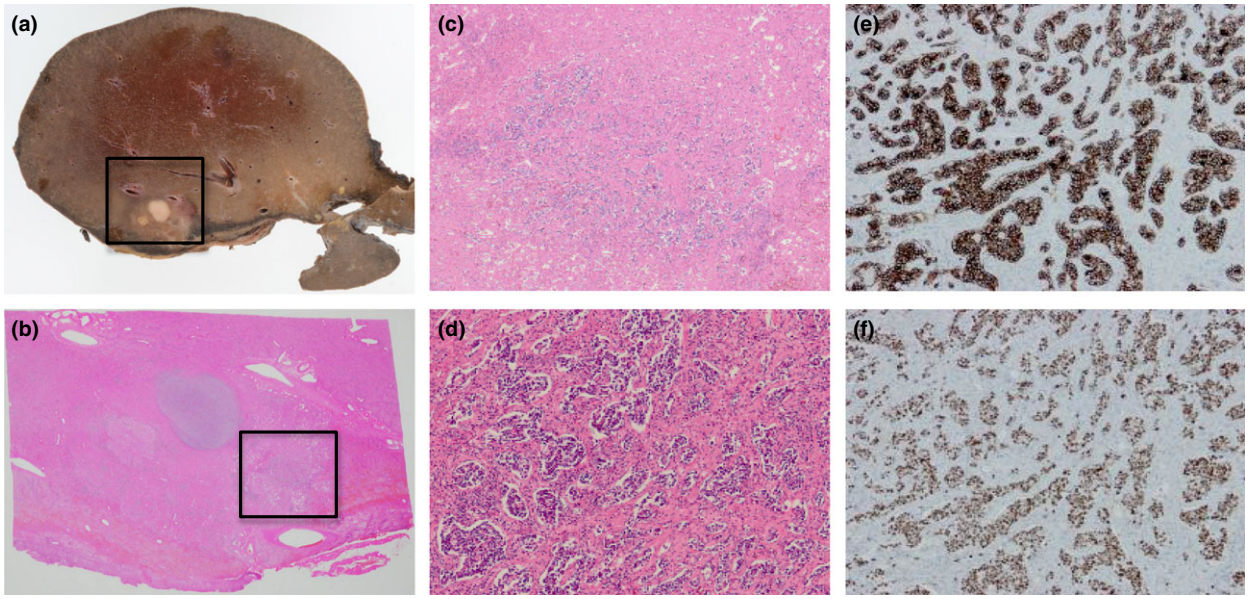

Figure 3 (a) Macroscopic image of the explanted liver. Histology of the explanted liver. (b) Hematoxylin and eosin staining of the square area in Fig. 3a (100×). (c) Hematoxylin and eosin staining of the square area in Fig. 3b (200×). (d) Hematoxylin and eosin (400×). (e) Atypical lymphocytes were positive for CD20. (f) Atypical lymphocytes were positive for Ki67.

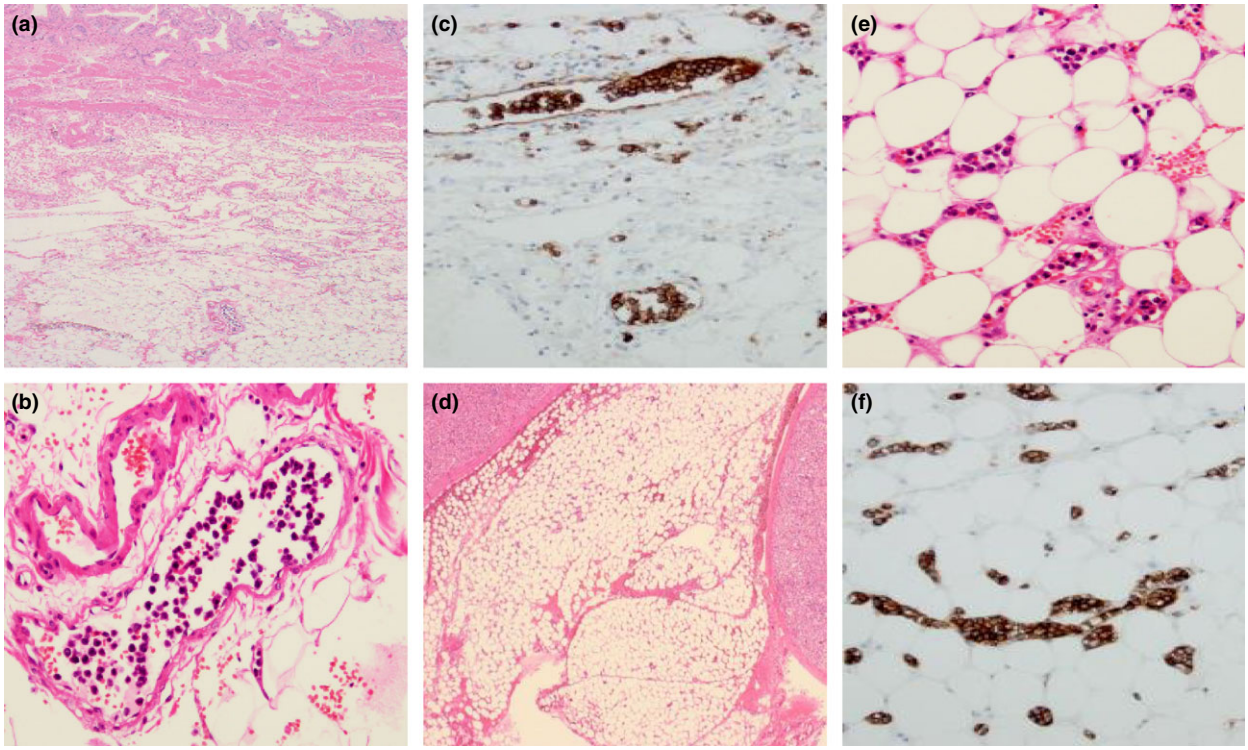

Figure 4 (a–c) Histology of the gallbladder. (a) Hematoxylin and eosin staining (200×). (b) Hematoxylin and eosin staining (400×). (c) Atypical lymphocytes were positive for CD20. (d–f) Histology of the spleen. (d) Hematoxylin and eosin staining (200×). (e) Hematoxylin and eosin staining (400×). (f) Atypical lymphocytes were positive for CD20.

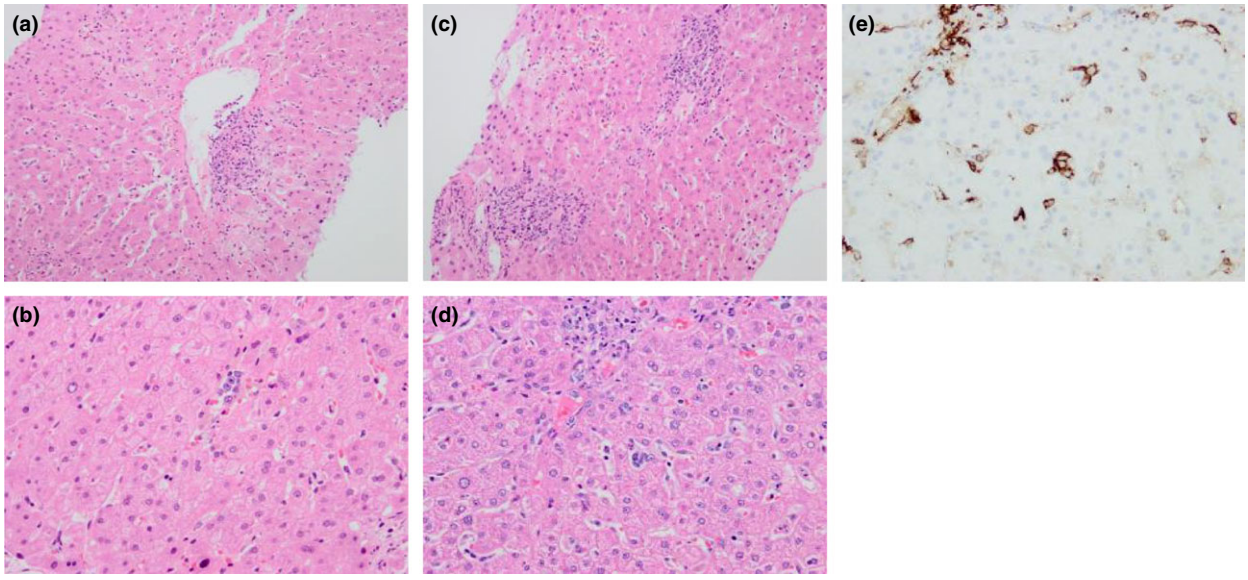

Figure 5 Histology of the transplanted liver. (a–d) Hematoxylin and eosin staining. (a) 200× (b) 400× (c) 200× (d) 400×. (e) Atypical lymphocytes were positive for CD20.

fulminant hepatitis. Because no lymphoma infiltration was detected in the hepatic parenchyma, we assumed that the comorbidity of fulminant hepatitis and IVL was coincidental.

The patient was successfully treated with R-CHOP once the diagnosis of IVL was made. Regarding clinical outcomes of IVL, Shimada *et al.* [13] performed a

retrospective analysis of IVL with and without rituximab-containing chemotherapy in 2008. They reported that the complete response rate is higher for patients receiving rituximab (82%) than for those not receiving rituximab (51%, $P = 0.01$) and concluded that the prognosis for IVL improved with rituximab. To date, there are no reports of IVL coexisting with fulminant hepatitis and that are being treated with R-CHOP after LT. Our experience suggests that R-CHOP could safely be administered to patients diagnosed with IVL even after LT.

Although the findings in this case may be skewed because of their rarity, they do suggest that the indications for LT to patients with either end-stage liver disease or fulminant hepatitis who were also preoperatively diagnosed with IVL may warrant further discussion. Historically, systemic lymphoma has been considered a contraindication to LT because of the risk of recurrence. If patients with IVL and liver disease cannot receive LT, they must be treated with standard chemotherapy, which is challenging for patients with a background of severe hepatic dysfunction. A substantial dose reduction may be required resulting in a poorer response rate. Based on the improved survival rates of patients with IVL patients in the rituximab era and our experience with the successful administration of R-CHOP treatment at an early stage after LT, we believe that these patients can be cured by performing LT before administering chemotherapy. Most recently, Schiano *et al.* [14] reported an ethical proposal on where to draw the line for high-risk LT candidates. They presented a case of lymphoma that presented with acute-on-chronic liver failure because of hepatitis B virus reactivation in the chemotherapy setting. The patient underwent LT. Although additional data are necessary to support our viewpoint, the previous report of liver failure that was successfully treated by LT [14] also supports our discussion.

In summary, we encountered an extremely rare case of IVL with fulminant hepatitis. Careful follow-up of the patient is still required; however, our case illustrates that improved survival may be possible for other patients with the same combination of conditions.

Authorship

KK, TF: participated in research design, collected data, performance of research, analysis, and writing of manuscript. YY, HH, TM, YK, HK, KY: collected data and performed analysis. YZ, TI: contributed important staining and performed analysis. YK: participated in research design and performance of research.

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