

# Liver Dysfunction and Thrombocytopenia Diagnosed as Intravascular Large B-cell Lymphoma Using a Timely and Accurate Transjugular Liver Biopsy

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## Abstract

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A 72-year-old man suffered from paraparesis with a sensory impairment and bladder and rectal disturbances. Magnetic resonance imaging T2-weighted images depicted a high-intensity lesion in the spinal cord that was consistent with myelitis. A blood examination revealed severe thrombocytopenia and liver dysfunction. No malignant cells were detected by peripheral smears or bone marrow biopsy. Systemic computed tomography detected hepatosplenomegaly and ascites but no lymphadenopathies. Transjugular liver biopsy (TJLB) safely confirmed a diagnosis of intravascular large B-cell lymphoma (IVLBCL), and the patient achieved a complete response following treatment with an appropriate chemotherapy. TJLB is therefore a timely and accurate diagnostic approach for IVLBCL, especially when a bleeding tendency and ascites are noted.

**Key words:** intravascular large B-cell lymphoma, transjugular liver biopsy, liver dysfunction, thrombocytopenia

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## Introduction

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Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal large B-cell lymphoma that is characterized by the proliferation of lymphoma cells within the lumina of small blood vessels, particularly the capillaries and the post-capillary venules, without an obvious extravascular tumor mass or detectable levels of circulating lymphoma cells in the peripheral blood (1). As IVLBCL is thought to be an aggressive lymphoma in the clinical setting, making a

timely diagnosis is extremely important since prompt treatment can improve the clinical outcome (2-4). However, no standard procedure for the diagnosis of IVLBCL has yet been established. We herein report a patient with IVLBCL and a bleeding tendency who initially presented with neurological symptoms. He was safely diagnosed using transjugular liver biopsy and successfully achieved a complete response (CR) following the administration of appropriate chemotherapy.

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**Table. Laboratory Data upon Admission**

<Peripheral blood>		<Chemistry/Serology>		<Viral markers>	
WBC	2,630 / $\mu$ L	TP	5.4 g/dL	HBsAg	0.1 C.O.I
seg	69 %	Alb	2.1 g/dL	HBsAb	0.1 mIU/mL
band	7 %	AST	42 IU/L	HBcAb	7.4 %INH
mono	6 %	ALT	91 IU/L	HCV	0.1 C.O.I
eosino	0 %	T-Bil	3.58 mg/dL	EBV-VL	<10 copy/ $\mu$ gDNA
baso	0 %	D-Bil	1.50 mg/dL		
lymph	17 %	ALP	204 IU/L	<Tumor markers>	
A-lymph	1 %	$\gamma$ GTP	25 IU/L	sIL-2R	14,408 IU/mL
RBC	396 $\times 10^4$ / $\mu$ L	LDH	261 IU/L	CEA	1.8 ng/mL
Hb	12.2 g/dL	BUN	31 mg/dL	CA19-9	3.8 IU/mL
Ht	37.1 %	Cr	0.56 mg/dL	AFP	3.1 ng/mL
MCV	93.7 fl	Na	140 mEq/L	PIVKA2	47 mAU/mL
Plt	1.1 $\times 10^4$ / $\mu$ L	K	4.2 mEq/L		
		Cl	103 mEq/L		
		Ferritin	511 ng/mL		
<Coagulation tests>		Haptoglobin	8.0 mg/dL		
PT	16.5 sec.	CRP	2.88 mg/dL		
APTT	47.3 sec.				
FDP-DD	7.4 ng/mL				

## Case Report

A 72-year-old man was admitted to our hospital, suffering from pain and palsy in both legs accompanied by muscle weakness and sensory impairment, as well as bladder and rectal disturbances and progressive thrombocytopenia. He had been taking intravenous pulse corticosteroids (two cycles of 1 g methylprednisolone per day for one to three days followed by oral prednisolone therapy) after thoracic spinal cord magnetic resonance imaging (MRI) revealed myelitis two months prior at his primary hospital. We noted the presence of non-medicated hypothyroidism. The patient did not have a history of neurological disease. No similar diseases were detected among his immediate family members.

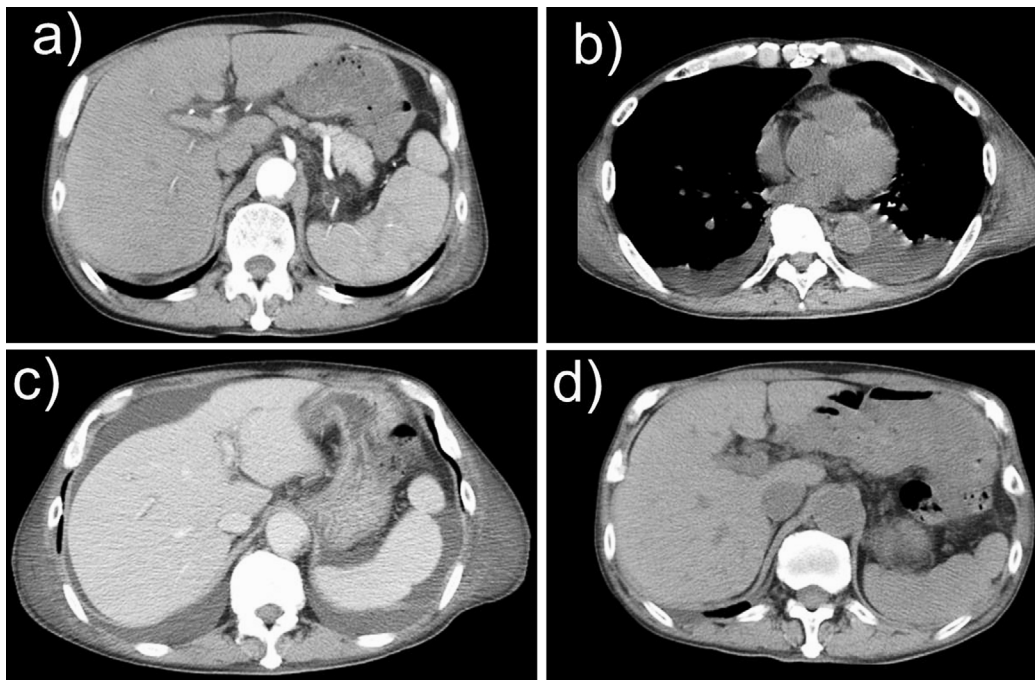
Upon examination, the patient was 166 cm tall, weighed 61 kg, and had a body mass index of 22.1 kg/m<sup>2</sup>. His peak body temperature was 38.7°C. He had a remittent fever and had presented with hepatosplenomegaly unaccompanied by systemic lymphadenopathy.

Blood examination (Table) showed leukocytopenia at 2,630/ $\mu$ L and severe thrombocytopenia at 1.1 $\times 10^4$ / $\mu$ L, but no abnormal cells were detected in repeated peripheral smears. Peripheral laboratory test results are shown in Table and are summarized as follows: aspartate aminotransferase (AST), 42 IU/L; alanine aminotransferase (ALT), 91 IU/L; lactate dehydrogenase (LDH), 261 IU/L; total bilirubin (T-Bil), 3.58 mg/dL; indirect bilirubin (I-Bil), 2.08 mg/dL; soluble IL-2 receptor (sIL-2R), 14,408 U/mL (at a prior point during intravenous pulse corticosteroid therapy; normal range, 135-421 U/mL). Epstein-Barr virus DNA in the whole blood was undetectable by real-time PCR. There were no findings that indicated either collagen disease or vasculitis. A contrast-enhanced computed tomography (CT) scan of the abdomen revealed hepatosplenomegaly (Fig. 1a). Neither lymphadenopathy nor an abnormal mass lesion was detected. A high-intensity lesion in the thoracic spinal cord was depicted by

T2-weighted MRI (Fig. 2). Brain examinations by MRI also showed a high-intensity lesion in the right parietal lobe by diffusion-weighted imaging, which indicated an acute phase of cerebral infarction. We strongly suspected IVLBCL from the patient's clinical features, in that he initially developed central nervous system (CNS) symptoms and that his condition rapidly deteriorated in spite of corticosteroid therapy. He also exhibited constitutional B symptoms accompanying hepatosplenomegaly without systemic lymphadenopathy, but we could not obtain any diagnostic findings from repeated bone marrow aspirations and biopsies or random skin biopsies.

Soon after hospitalization, the patient's general condition began to worsen. A chest CT depicted a pleural effusion, and an abdominal CT revealed hepatosplenomegaly and ascites (Fig. 1b, c). A fludeoxyglucose (18F)-positron emission tomography (FDG-PET)/CT scan could not be performed as a measure of disease activity, and percutaneous liver biopsy was contraindicated due to the severe thrombocytopenia and the existence of ascites. Therefore, we performed a transjugular liver biopsy. First, a 9-F vascular sheath was introduced into the right jugular vein. The right hepatic vein (RHV) was cannulated with a 4-F Cobra catheter (Terumo Clinical Supply, Gifu, Japan) and a 0.035-inch guide wire. Next, a ROSCH-UCHIDA transjugular liver access and biopsy set catheter (COOK Medical, Bloomington, IN, USA) was inserted into the RHV over the guide wire. We thus obtained five biopsy samples after confirming the location of the catheter at the RHV using X-ray fluoroscopy (Fig. 3a) and ultrasonography (Fig. 3b).

Liver biopsy specimens revealed the infiltration of large lymphoma cells with irregularly shaped nuclei in the sinusoidal, portal and central venous regions (Fig. 4a, b). These cells were positive for an anti-CD20 antibody (Fig. 4c) but negative for CD3 (Fig. 4d), CD5, TIA1, Granzyme B and EBER immunohistochemical staining. These findings were consistent with a diagnosis of IVLBCL.

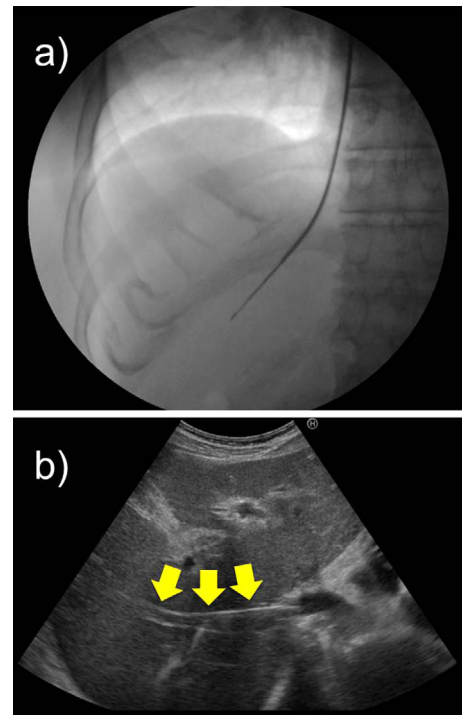


**Figure 1.** Computed tomography (CT) findings. (a) Abdominal CT upon admission showed hepatosplenomegaly. Neither lymphadenopathy nor an abnormal mass lesion was detected. (b) Chest CT immediately prior to liver biopsy depicted a pleural effusion. (c) Abdominal CT immediately prior to liver biopsy revealed hepatosplenomegaly and ascites. (d) Abdominal CT after achieving a complete response showed the improvement of the hepatosplenomegaly.

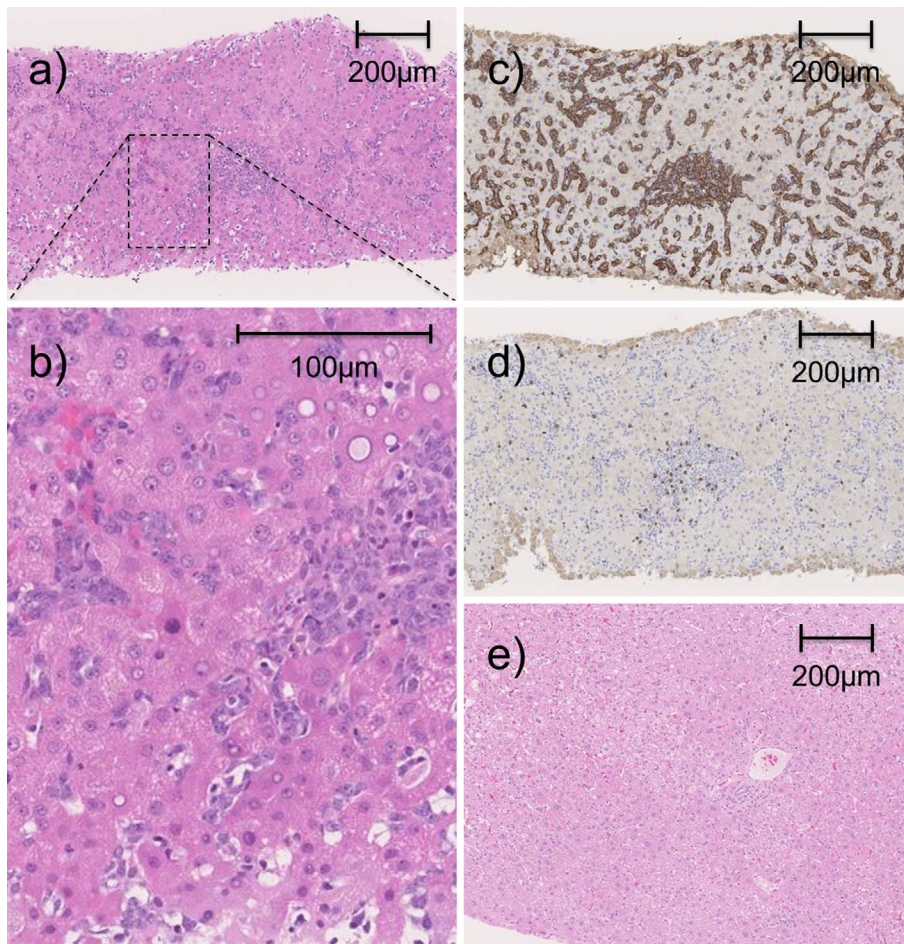


**Figure 2.** T2-weighted magnetic resonance imaging of the spinal cord showed a high-intensity lesion in Th7-9 (yellow circle), indicating the presence of myelitis. The patient presented with progressive weakness below the level of the lesion with accompanying sensory loss and bladder dysfunction.

The patient was immediately started on a modified CHOP regimen (1,200 mg cyclophosphamide, day 1; 80 mg doxorubicin, day 1; 60 mg PSL, days 1-5; vincristine was not administered due to severe neuropathy), and special attention was paid to the possibility of tumor lysis syndrome (5, 6). Although he developed complications with pneumocystis carinii pneumonia and cytomegalovirus reactivation during the first course of therapy, these were cured with sulfamethoxazole/trimethoprim and ganciclovir,



**Figure 3.** Transjugular liver biopsy was performed using an ultrasonographic guidance procedure. (a) A ROSCH-UCHIDA transjugular liver access and biopsy set catheter was inserted into the right hepatic vein (RHV) over a guide wire. (b) The location of the catheter was confirmed at the RHV by ultrasonography (yellow arrows).



**Figure 4.** (a: low-power field, b: high-power field) A microscopic examination of the liver biopsy sections revealed the presence of large tumor cells in the sinusoids of the liver. These cells exhibited irregularly shaped round or ovoid nuclei and abundant pale basophilic cytoplasm (Hematoxylin and Eosin staining). (c) The tumor cells were identified by positive immunohistochemical staining for CD20. (d) The tumor cells were negative for CD3 staining. (e) The liver biopsy specimens taken at the end of chemotherapy confirmed that the tumor cells had disappeared from the sinusoids, which was consistent with a histological complete response.

respectively. We then switched to modified R-CHOP therapy with the addition of the recombinant anti-CD20 antibody rituximab for ensuing treatments. Subjective and objective neurological findings, such as numbness in the lower extremities, showed a gradual improvement. MRI examination after the third course of chemotherapy revealed complete disappearance of the abnormal lesions from the spinal cord. The patient's rectal sphincter dysfunction showed improvement after the fourth course of chemotherapy, but his bladder disturbance remained. He was discharged from our hospital on foot following the fifth course of the chemotherapy and later uneventfully received three additional courses of R-CHOP in our hospital's outpatient chemotherapy unit. After the eighth course of chemotherapy, FDG-PET/CT showed no residual lesions and the percutaneous liver biopsy specimens revealed no infiltration of malignant lymphoma cells (Fig. 4e). These findings were consistent with the achievement of a CR.

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## Discussion

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IVLBCL is an extremely rare subtype of large B-cell lymphoma for which most data are derived from case reports and are based on only a small group of patients. Therefore, the epidemiology of IVLBCL is unknown, including its true incidence. Moreover, the clinical presentation of this condition appears to be nonspecific, and individual presentations vary tremendously due to the variety of organs involved, although most patients with IVLBCL (55-85%) show constitutional B symptoms, such as fever, night sweats, and weight loss (2-4, 7). Two major patterns of clinical presentation have been recognized for IVLBCL: those of patients in Asian countries vs. their Western counterparts. Asian patients frequently present with the involvement of the liver (55%), bone marrow (75%), and spleen (67%) (2, 4, 7, 8), whereas CNS involvement (27%) and cutaneous lesions (15%) are far less common in Asians than in non-

Asians (2, 4, 7, 9). It should be considered as uncommon that this Asian variant IVLBCL patient initially showed neurological symptoms. The poor prognosis of IVLBCL might be partially related to frequent delays in diagnosis due to its non-specific nature, although survival rates have been shown to increase in those patients who undergo rituximab-containing chemotherapies (2, 3). It has been previously reported that random skin biopsies, regardless of the presence or absence of skin lesions, were comparably sensitive to bone marrow biopsy in the diagnosis of IVLBCL (10). Kaku et al. also presented an IVLBCL case that was successfully diagnosed by random transbronchial lung biopsies on the patient who exhibited hypoxia and an increased alveolar-arterial oxygen difference (A-aDO<sub>2</sub>) despite having no abnormal findings on chest CT (11). Moreover, Higurashi et al. described a patient showing hepatosplenomegaly who was diagnosed as having IVLBCL by liver biopsy (12). Therefore, repeatable histological biopsies of the suspectedly involved organs are needed for a successful diagnosis. We conducted a successful transjugular liver biopsy for the timely diagnosis and treatment of IVLBCL in the present case. We proceeded with the liver biopsy as we could obtain no diagnostic findings using less invasive diagnostic approaches, such as bone marrow and skin biopsies, and our patient showed liver dysfunction with hepatomegaly and a rapidly deteriorating state.

Percutaneous liver biopsy has been proven to be fast, safe and efficient, to the point of becoming the gold standard for liver tissue sampling in patients showing liver dysfunction. However, this technique involves the transection of the liver capsule, which puts patients with thrombocytopenia and/or coagulopathy at an increased risk for intraperitoneal hemorrhaging (13, 14). Thrombocytopenia is present in 76% of the Japanese IVLBCL patients, as compared with only 29% of Western patients (7-9), and hemophagocytic syndrome can be seen in as many as 59% of patients with IVLBCL (2). Consequently, alternative techniques, such as transjugular liver biopsy, have been developed to permit harvesting of liver tissue in patients who are under contraindications to the percutaneous procedure. In general, transjugular liver biopsy is diagnostic in nature for 85-100% of several disease cases (15). Unlike percutaneous biopsy, this approach accesses the liver parenchyma through the superior vena cava and hepatic vein, and obtains hepatic tissue without traversing the liver capsule. Any possible bleeding from the biopsy site is directed into the access vein, thereby minimizing the risk of intraperitoneal hemorrhaging. Therefore, transjugular liver biopsy is considered to be safe and well tolerated, and should generally be the first-line option for patients in whom the percutaneous approach is contraindicated, especially for IVLBCL patients such as ours who are complicated with thrombocytopenia and coagulopathy. However, since it has also been reported that the overall complication rate of transjugular liver biopsy ranges from 1-20% based on conditions including hemoperitoneum, hemobilia and fistulas between the hepatic vein, hepatic artery, portal

vein and biliary system, we assured the safety of our patient with ultrasonographic guidance, as had been reported previously (15).

If a timely diagnosis is made and an anthracycline-based chemotherapy, such as CHOP or R-CHOP, is instituted, then many patients achieve a CR at a rate of 60% rate and exhibit an estimated 3-year overall survival expectancy of greater than 30%, implying that long-term survival is possible for IVLBCL (2). We safely diagnosed our patient by transjugular liver biopsy and immediately commenced the administration of appropriate treatment, thereby obtaining a favorable outcome. However, we will continue to follow up this case since it has been reported that CNS symptoms tend to recur within a short period of time in patients with CNS involvement at diagnosis (4).

In conclusion, clinicians should keep transjugular liver biopsy in mind as a timely and accurate diagnostic approach for IVLBCL, especially when the patient shows hepatomegaly and liver dysfunction and is complicated with ascites and a bleeding tendency, such as thrombocytopenia or coagulopathy.

**The authors state that they have no Conflict of Interest (COI).**

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