

Intravascular large b-cell lymphoma diagnosed via transjugular liver biopsy in a patient with liver dysfunction and thrombocytopenia

A Case Report

Mi-Jung Kim, MD^a, Ho-Sung Park, MD, PhD^b, Ho-Young Yhim, MD, PhD^{a,c,*}

Abstract

Rationale: Intravascular large B-cell lymphoma (IVLBCL) is an extremely rare subtype of large B-cell lymphoma characterized by the presence of lymphoma cells within the lumen of small blood vessels. IVLBCL presents with nonspecific symptoms such as fever, weight loss, and bleeding. Because of its rarity and unremarkable clinical presentation, a timely diagnosis is very challenging.

Patient concerns: A 71-year-old Korean man complained of fever, but apart from pretibial pitting edema and mild thrombocytopenia, the physical examination and laboratory test findings were unremarkable.

Diagnoses: A bone marrow biopsy was also nonspecific. The fever persisted and his thrombocytopenia became more pronounced, prompting further laboratory tests that indicated infiltrative liver disease.

Interventions: Because of coagulopathy, a liver biopsy was performed using a transjugular instead of a percutaneous approach.

Outcomes: The procedure was performed without complications, and the pathologic examination findings were consistent with IVLBCL. Unfortunately, the patient died because of disease progression before treatment could be administered.

Lessons: Given that an early diagnosis can affect the prognosis of IVLBCL, quickly and safely obtaining a biopsy specimen is very important. The case presented here shows that a liver biopsy obtained via a transjugular approach is safe and could be preferentially considered when there is a high risk for bleeding complications.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CT = computed tomography, IVLBCL = intravascular large B-cell lymphoma, LDH = lactate dehydrogenase.

Keywords: biopsy, case report, intravascular large B-cell lymphoma, liver dysfunction, random skin, transjugular liver biopsy

1. Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare, but aggressive lymphoma. Several studies recently reported that rituximab-based combination chemotherapy was effective in the treatment of IVLBCL.^[1–5] With such potential for improved clinical outcomes, early diagnosis is very important. However, there is no established, standard procedure to diagnose IVLBCL.^[3] In part, this is because IVLBCL presents with

nonspecific, general symptoms and primarily involves the extranodal organs, including the liver, lungs, and central nervous system.^[1,6,7] A substantial number of patients show marked thrombocytopenia at presentation, causing physicians to hesitate to perform a biopsy and a subsequent delay in diagnosis.^[8,9]

Here, we describe a patient who presented with nonspecific symptoms. The disease progressed with hepatosplenomegaly, and a profound bleeding tendency associated with severe thrombocytopenia. IVLBCL was successfully diagnosed using a transjugular approach liver biopsy.

2. Case report

A 71-year-old man was transferred to the emergency room because of a persistent fever. One month previously, he had visited a different hospital for the same reason and was administered antituberculous therapy because of suspected pulmonary tuberculosis as indicated on a chest computed tomography (CT) scan. Right after taking this medication, thrombocytopenia (57,000 cells/mm³), anemia (10 g/dL), and gastrointestinal discomfort developed, and medication was stopped. Three weeks later, he regained his fever and experienced nausea and vomiting. Treatment with broad-spectrum antibiotics was ineffective. At the time of emergency room admission, his major symptoms were a fever up to 40°C and chills. The physical examination findings were normal, except for pretibial pitting edema (++) in both legs. The spleen was not palpable and not enlarged on abdominal CT (Fig. 1A). Cultures of blood, urine, and sputum were subjected to tests for influenza virus, urinary

Editor: Weimin Guo.

This study was approved by the Chonbuk National University Hospital Institutional Review Board, which waived the requirement for informed consent.

The authors report no conflicts of interest.

^a Department of Internal Medicine, ^b Department of Pathology, Chonbuk National University Medical School, ^c Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Republic of Korea.

* Correspondence: Ho-Young Yhim, Department of Internal Medicine, Chonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju 561-712, Republic of Korea (e-mail: yhimhy@jbnu.ac.kr).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2017) 96:19(e6925)

Received: 12 September 2016 / Received in final form: 12 January 2017 /

Accepted: 25 April 2017

<http://dx.doi.org/10.1097/MD.0000000000006925>

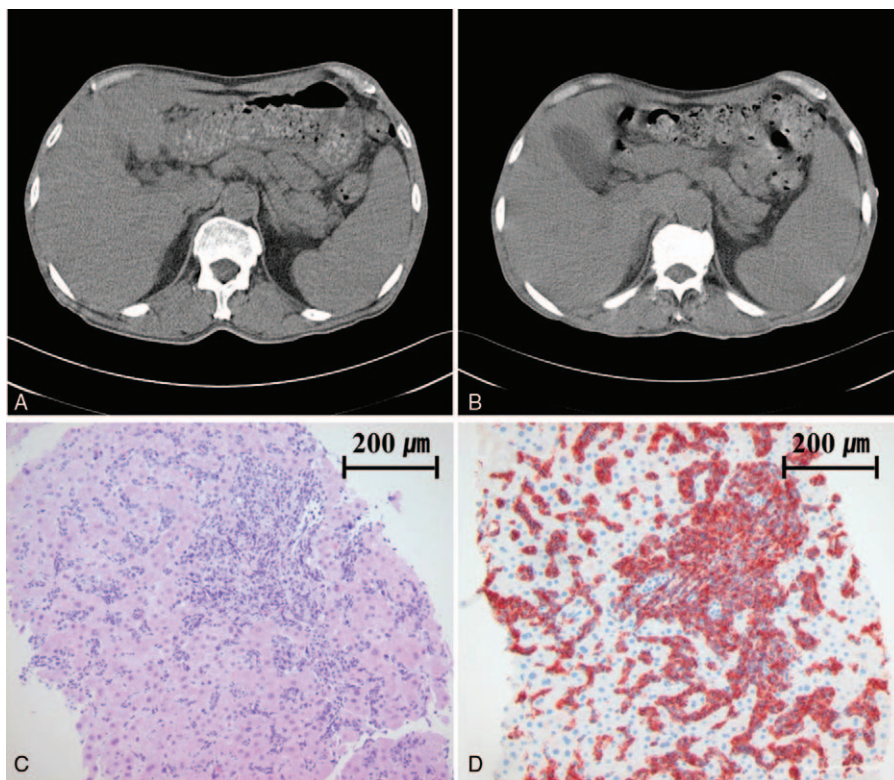


Figure 1. Computed tomography (CT) findings. Microscopic examination of liver biopsy sections shows the presence of large tumor cells in sinusoids of the liver. (A) Initial abdominal CT shows no splenomegaly. (B) After 2–3 weeks, splenomegaly is visible. (C) Large tumor cells in the liver sinusoid show irregularly shaped, round, and ovoid nuclei (hematoxylin & eosin staining). (D) The tumor cells are positive for CD20 staining.

streptococcus pneumonia antigen, Hantaan virus, *Tsutsugamushi orientalis*, the human immunodeficiency virus, malaria, and the presence of antinuclear antibodies; all of the results were negative. Ferritin was 98 ng/mL and fibrinogen was 257 mg/dL. The initial blood chemistry tests showed a total bilirubin level of 0.67 mg/dL, aspartate aminotransferase (AST) of 35 IU/L, alanine aminotransferase (ALT) of 14 IU/L, alkaline phosphatase (ALP) of 252 IU/L, and lactate dehydrogenase (LDH) of 894 IU/L. Peripheral blood smears repeatedly revealed leukopenia with neutropenia and thrombocytopenia without clinical significance. Bone marrow examination revealed near-normal trilineage hematopoiesis, except for iron deficiency anemia.

Approximately 2 to 3 weeks later, blood chemistry results were elevated, with a total bilirubin of 1.68 mg/dL, AST of 48 IU/L, ALT of 43 IU/L, ALP of 1331 IU/L, gamma-glutamyltransferase of 235 IU/L, and LDH of 1616 IU/L. These results led us to suspect an infiltrative liver disease; therefore, the abdominal CT was repeated and revealed hepatosplenomegaly, which was not observed initially (Fig. 1B). Also, his thrombocytopenia and anemia (8 g/dL) had worsened and his ferritin was elevated up to 1585 ng/mL. Hemaphagocytic lymphohistiocytosis was suspected based on these findings, but soluble CD25 and NK cell activity were not able to be measured at our hospital, which was the only available laboratory in Korea.

A liver biopsy was necessary to confirm a diagnosis, but the traditional percutaneous liver biopsy approach was not performed because severe thrombocytopenia (15,000 cells/mm³), which was unresponsive to repeated transfusions and, increased the risk of bleeding complications. Instead, we performed a transjugular liver biopsy with fluoroscopic guidance. This

alternative approach accessed the liver parenchyma through the superior vena cava and hepatic vein to obtain hepatic tissue without liver capsule breaks (Fig. 2).

The liver biopsy specimen revealed infiltration of large lymphoma cells with irregular shaped nuclei in the sinusoidal, portal, and central venous regions.^[5] Lymphoma cells were positive for anti-CD20 antibody, but negative for CD3 and CD5 (Figs. 1C and D).^[5,8,10] All findings were consistent with IVLBCL. Unfortunately, the patient died because of the progression of the disease before treatment could be administered.

3. Discussion

IVLBCL is characterized by intravascular proliferation of neoplastic lymphoid cells with a systemic dissemination, and it is extremely rare.^[11] The most common symptoms are B symptoms such as fever, night sweats, and weight loss, as well as progressive neurologic symptoms, skin lesions, general fatigue, gastrointestinal discomfort, and edema.^[4,5,12,13] There are 2 major patterns of clinical presentation. For white patients, it is usually accompanied by skin and neurological symptoms, whereas Asian patients predominantly exhibit involvement of the liver, bone marrow, and spleen.^[2,4,5,9,14] Our patient had unremarkable signs and symptoms at presentation, and it was not until later that liver involvement was suspected. Diagnosis was delayed because of nonspecific symptoms and clinical signs and because the standard method of liver biopsy, the percutaneous approach, was contraindicated by progressive coagulopathy.

Liver biopsies can be performed using percutaneous, transjugular, or laparoscopic approaches. Each method has advan-

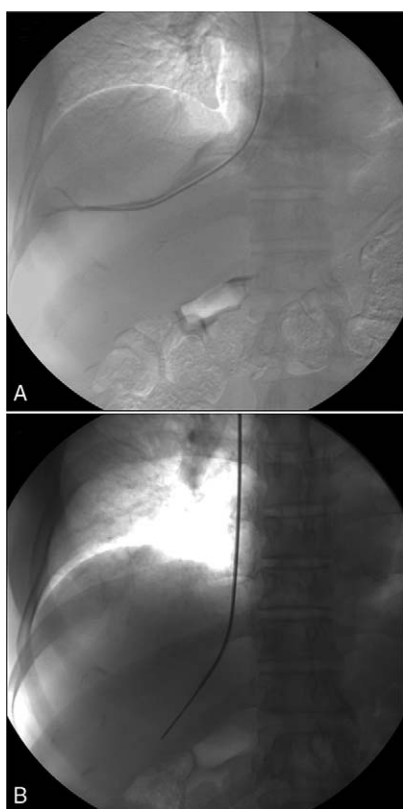


Figure 2. A transjugular liver biopsy is performed using a fluoroscopic guidance procedure. (A) The location of the catheter is confirmed at the right hepatic vein by fluoroscopy. (B) A Rösch-Uchida transjugular liver access set (Cook Medical, Bloomington, IN) is inserted into the right hepatic vein.

tages and disadvantages, so physicians should choose the approach that maximizes the diagnostic achievement and minimizes the number of complications. Among these approaches, transjugular liver biopsies have been limited to patients with end-stage cirrhotic liver disease, acute liver failure, or congenital clotting disorders.^[15,16] This is because it is thought to be a “second class” procedure, providing smaller and more fragmented specimens that might be difficult to examine.^[15,16] However, transjugular liver biopsies have been shown to be equivalent to percutaneous biopsies in terms of safety and have a histologic diagnostic achievement of >90%.^[15,16] Thus, it is possible to obtain adequate tissue to diagnose patients using transjugular liver biopsies.^[15–17] It has also been reported that the complication rate of transjugular liver biopsies is relatively low (7%) with few major events, such as peritoneal hemorrhage and ventricular arrhythmia, and the mortality rate is <0.1%. In contrast, percutaneous liver biopsies have an increased risk of bleeding (as high as 12.5%) and a higher mortality (1%).^[15,15,17] Because a transjugular liver biopsy is performed through the vascular system, any bleeding related to the procedure is directed into the access vessels, possibly decreasing the major bleeding risk (hemoperitoneum).^[15] Moreover, a transjugular approach lends itself to immediate embolization to control procedure-related bleeding. Generally, it can be performed for patients with severe coagulopathy, ascites, and acute liver failure.^[15,16,17] A transjugular liver biopsy can be the first option to diagnose patients with severe thrombocytopenia because it is a safe and adequate diagnostic procedure.

It is difficult to diagnose IVLBCL timely enough to treat patients properly because there are few disease-specific signs and symptoms. To confirm IVLBCL, it is necessary to perform histology, so a biopsy from an affected organ is necessary.^[17] However, if there are no indicated sites from which to take a biopsy, a random skin biopsy can be considered.^[1,3,6–8] In various reports, a random skin biopsy is described as useful, safe, and even comparable to a bone marrow biopsy whether skin lesions are present or not.^[18] Because a random skin biopsy is a minimally invasive procedure and has little risk of bleeding, it can be performed on patients who have thrombocytopenia and coagulation abnormalities, similar to our patient. Therefore, a random skin biopsy could be another option when intravascular lymphoma is suspected in patients who have a high bleeding risk and no suspicion of the involvement of particular organs.^[18] In our case, a random skin biopsy was not performed because the possibility of IVLBCL was not considered.

IVLBCL was considered invariably fatal in the past, but there have been many studies recently demonstrating systemic chemotherapy; R-CHOP improves the long term survival of some patients in comparison with untreated patients. In addition, high-dose chemotherapy with autologous hematopoietic transplantation should be considered especially for young patients to achieve complete responses.^[2,4,5,13] For our patient, systemic chemotherapy with R-CHOP could have been administered.

4. Conclusion

We present a rare case of IVLBCL, diagnosed too late to treat the patient. A transjugular liver biopsy was used to confirm the diagnosis but was delayed because of a low index of suspicion and complicating coagulopathy. Because rituximab-based combination chemotherapy has been effective in the treatment of IVLBCL, it is crucial to get histology promptly when lymphoid malignancy infiltrating liver diseases, such as IVLBCL, are suspected. This case showed that a transjugular liver biopsy was safe and should be considered when there is a high risk for bleeding complications from a percutaneous biopsy.

References

- Gill S, Melosky B, Haley L, et al. Use of random skin biopsy to diagnose intravascular lymphoma presenting as fever of unknown origin. *Am J Med* 2003;114:56–8.
- Khan MS, McCubbin M, Nand S. Intravascular large B-cell lymphoma a difficult diagnostic challenge. *J Invest Med* 2014;2:1–3.
- Le K, Lim A, Bullpitt P, et al. Intravascular B-cell lymphoma diagnosed by skin biopsy. *Australas J Dermatol* 2005;46:261–5.
- Liu C, Lai N, Zhou Y, et al. Intravascular large B-cell lymphoma confirmed by lung biopsy. *Int J Clin Exp Pathol* 2014;7:6301.
- Sekiguchi N, Joshita S, Yoshida T, et al. Liver dysfunction and thrombocytopenia diagnosed as intravascular large B-cell lymphoma using a timely and accurate transjugular liver biopsy. *Intern Med (Tokyo, Jpn)* 2013;52:1903–8.
- Ikoma N, Manabe Y, Yamaoka H, et al. Random skin biopsy of intravascular large B-cell lymphoma: a case report. *Tokai J Exp Clin Med* 2012;37:75–6.
- Le EN, Gerstenblith MR, Gelber AC, et al. The use of blind skin biopsy in the diagnosis of intravascular B-cell lymphoma. *J Am Acad Dermatol* 2008;59:148–51.
- Matsue K, Asada N, Odawara J, et al. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. *Ann Hematol* 2011;90:417–21.
- Maekawa T, Komine M, Murata S, et al. Random skin biopsy of patients with intravascular large B-cell lymphoma associated with thrombocytopenia and coagulation abnormalities: proposal of a modified biopsy method. *J Dermatol* 2015;42:318–21.

- [10] Khojeini EV, Song JY. Intravascular large B-cell lymphoma presenting as interstitial lung disease. *Case Rep Pathol* 2014;2014:1–3.
- [11] Ramkumar B, Hutchison R, Khadim H, et al. Intravascular large B-cell lymphoma—a diagnostic dilemma. *Clin Lymphoma Myeloma Leuk* 2013;13:e18–21.
- [12] Adachi Y, Kosami K, Mizuta N, et al. Benefits of skin biopsy of senile hemangioma in intravascular large B-cell lymphoma: a case report and review of the literature. *Oncol Lett* 2014;7:2003–6.
- [13] Feci L, Pellegrino M, Mancini V, et al. Skin biopsy leading to diagnosis of diffuse intravascular B-cell lymphoma presenting as a fever of unknown origin. *J Eur Acad Dermatol Venereol* 2016;30:883–4.
- [14] Kasuya A, Hashizume H, Takigawa M. Early diagnosis of recurrent diffuse large B-cell lymphoma showing intravascular lymphoma by random skin biopsy. *J Dermatol* 2011;38:571–4.
- [15] Alessandria C, Debernardi-Venon W, Rizzetto M, et al. Transjugular liver biopsy: a relatively simple procedure with an indefinite past and an expected brilliant future. *J Hepatol* 2008;48:171–2.
- [16] Kalambokis G, Manousou P, Vibhakorn S, et al. Transjugular liver biopsy—indications, adequacy, quality of specimens, and complications—a systematic review. *J Hepatol* 2007;47:284–94.
- [17] Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001;344:495–500.