Contrast-Enhanced Ultrasonography in Diagnosing Intravascular Large B-Cell Lymphoma Infiltrating Liver Sinusoids

ABDEF 1 Hikari Ota
ABD 2 Satoshi Nakayama
BD 3 Hiroaki Takeo
BD 4 Sadahiro Watanabe
AD 1 Kazuhiro Masuoka

1 Department of Hematology, Mishuku Hospital, Tokyo, Japan
2 Department of Gastroenterology, Mishuku Hospital, Tokyo, Japan
3 Department of Pathology, Japan Self-Defense Forces Central Hospital, Tokyo, Japan
4 Department of Radiology, Japan Self-Defense Forces Central Hospital, Tokyo, Japan

Corresponding Author: Hikari Ota, e-mail: h-ota@mishuku.gr.jp

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Patient: Female, 83-year-old
Final Diagnosis: Intravascular large B-cell lymphoma
Symptoms: Fever
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease
Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells within vasculature. This presents a diagnostic challenge due to non-specific symptoms and lack of tumor formation. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) provides useful information in diagnosing FDG-avid lymphoma, but is not specific to IVLBCL. Contrast-enhanced ultrasonography (CEUS) is useful in evaluating focal liver lesions; however, its efficacy in diagnosing IVLBCL involving the liver remains unknown.

Case Report: We report the case of an 83-year-old woman presenting with fever, pancytopenia, liver dysfunction, and elevated LD and soluble interleukin-2 receptor levels. PET-CT showed multiple uptake lesions in the liver. We performed CEUS with Sonazoid® to evaluate the mass-like lesions; however, no nodular lesions were observed in B mode images. Systemic enhancement was seen in the early phase but no defect was observed in the post-vascular phase. The latter finding suggested preserved Kupffer cells function, excluding tumor-forming lymphoma and liver metastases. Suspecting IVLBCL, we performed a bone marrow examination, which showed sinusoidal infiltration of large neoplastic cells positive for CD20. The patient’s condition deteriorated rapidly and she died 2 days after the examination. Autopsy revealed diffuse infiltration of lymphoma cells into liver sinusoids with preserved Kupffer cells, leading to the diagnosis of IVLBCL.

Conclusions: Our case shows that CEUS can distinguish IVLBCL from mass-forming lymphoma based on the absence of a defect in the post-vascular phase in a patient with clinically and radiographically suspected lymphoma involving the liver. This can assist clinicians to select appropriate lesions for biopsy.

Keywords: Lymphoma • Capillaries • Kupffer Cells • Positron Emission Tomography Computed Tomography • Ultrasonography • Sonazoid

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells within vasculature, particularly in capillaries [1]. Well-known causes of lymphoma are immunodeficiency and autoimmune disorders, often in association with Epstein-Barr virus, but specific risk factors for IVLBCL have not been determined [2]. B symptoms (fever, night sweats, and unintentional weight loss), hepatosplenomegaly, and anemia/thrombocytopenia are frequently observed in IVLBCL [3], although these are non-specific. IVLBCL frequently involves organs such as bone marrow, liver, spleen, skin, and lungs [3]; there is usually no tumor formation or lymphadenopathy, making it a diagnostic challenge with conventional imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI).

18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has been useful for diagnosing IVLBCL. In a patient with fever of unknown origin and elevated lactate dehydrogenase (LD), high-uptake lesions in FDG PET/CT may suggest IVLBCL [4-6]. However, high-uptake lesions can also be observed in patients with other FDG-avid, mass-forming lymphomas and advanced cancers, and thus are not specific to IVLBCL. Therefore, an imaging modality that can be used to evaluate, or rule out, solid tumor formation may be effective in diagnosing IVLBCL if used in tandem with FDG-PET.

Contrast-enhanced ultrasonography (CEUS) is currently used to evaluate focal liver lesions [7]. CEUS enables real-time visualization of contrast-enhancement patterns during all vascular phases (arterial, portal-venous, and late phase). Furthermore, CEUS using Sonazoid® (Perflubutane; GE Healthcare Pharma, Tokyo, Japan) can visualize a post-vascular phase (Kupffer phase) because the contrast agent is phagocytosed by Kupffer cells [7,8]. Since malignant lesions do not possess Kupffer cells, the absence of Kupffer cells causes a defect in Sonazoid uptake in the post-vascular phase and this contributes to localization and diagnosis of malignant focal liver lesions [7,8]. However, little is known about the diagnostic ability of CEUS in IVLBCL [9] and its efficacy has not been clarified. If CEUS can suggest IVLBCL, it would help clinicians consider a less invasive biopsy site such as bone marrow and/or skin instead of the liver to obtain histological diagnosis [10-12].

Here, we present a case of IVLBCL that showed multiple FDG uptake lesions in the liver without showing any defects in the post-vascular phase of CEUS. CEUS is useful in assessing suspected IVLBCL involvement in the liver.

Case Report

An 83-year-old Japanese woman with a history of resection of an ascending colon tumor of high-grade adenoma and cholecystitis reported having fever and general fatigue. Physical examination showed neither lymphadenopathy nor skin eruption. No specific signs of infection or autoimmune diseases were observed. Laboratory data showed pancytopenia (white blood cell count: 2590/µL with 69% neutrophils, 11% monocytes and 20% lymphocytes, hemoglobin level: 8.8 g/dL, platelet count: 7.1×10^4/µL, liver dysfunction (total bilirubin level: 1.9 mg/dL [normal range 0.3-1.2 mg/dL], AST: 100 IU/L [normal range 10-40 IU/L], ALT: 10 IU/L [normal range 5-40 IU/L], ALP: 252 IU/L [normal range 38-113 IU/L] and elevation of LD: 2338 IU/L [normal range 124-222 IU/L], and soluble interleukin-2 receptor: 2060 U/mL (normal range 122-496 U/mL). The data for beta-2 microglobulin were not available. A chest X-ray showed a nodule in the upper lobe of the right lung. A plain CT scan showed low-density areas in the liver (Figure 1) and the right lung nodule. FDG PET/CT showed multiple uptake lesions in the liver and bone marrow, and focal uptake of the right lung nodule, as well as the surgical scar in the ascending colon (Figure 2A, 2B). Colonoscopy detected no abnormal lesions. Tumor markers of carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), and neuron-specific enolase (NSE) were negative. Given these findings, malignant lymphoma such as diffuse large B-cell lymphoma, IVLCL, or lung cancer with multiple metastasis were considered as differential diagnoses. Because she was unable to tolerate an enhanced CT scan and an MRI was not immediately available, we performed CEUS to evaluate the mass-like lesions; however, no nodular lesion was observed in B mode images of both liver lobes (Figure 3A). Systemic enhancement was seen in the early vascular phase but no defect.
was observed in the post-vascular phase (Figure 3B-3D). The latter finding suggested preserved Kupffer cell function of the whole liver, excluding tumor-forming lymphoma and liver metastases. With high suspicion of IVLBCL, we performed a bone marrow examination; the results revealed sinusoidal infiltration of large neoplastic lymphoid cells with immunohistochemical expression positive for CD20, CD79a, CD5, CD10, MUM1, BCL-2, and BCL-6, and negative for CD3, Cyclin D-1, CD15, CD30, and ALK. The patient's condition deteriorated rapidly and she died 2 days after the bone marrow examination.

Autopsy showed ill-defined, pale white changes in both liver lobes (Figure 4). Histology confirmed the generalized proliferation of large neoplastic B-cells within small vessels and/or sinusoids of the liver (Figure 5A-SC), spleen, bone marrow, lymph nodes, lung, pleura, epicardium, esophagus, duodenum, pancreas, kidneys, and left adrenal gland, leading to the diagnosis of IVLBCL. In addition to tumor cells, CD68-positive Kupffer cells were also observed in liver sinusoids (Figure 5D), and some of the Kupffer cells showed evidence of hemophagocytosis. There was no distinct pathological difference between samples of the 2 liver lobes. The right lung nodule was found to be keratinized squamous cell carcinoma with no distant metastasis. The cause of death was concluded to be multiple-organ failure caused by IVLBCL.

Discussion

We present a case of IVLBCL that showed multiple FDG uptake lesions in the liver without showing any defects in the post-vascular phase of CEUS. Diffuse infiltration of tumor cells into the liver sinusoids and preservation of Kupffer cells were confirmed at autopsy.

Our case showed multiple FDG uptake lesions in the liver and bone marrow, suggesting lymphoma. PET-CT is recommended for staging in FDG-avid lymphoma [13] and this has also been useful in IVLBCL. According to the reported cases of IVLBCL showing FDG uptake in the liver (Table 1) [6,9,14-16], imaging patterns of hepatic involvement can present in 2 forms: multiple lesions within the liver or diffuse uptake throughout the entire liver. The variability in the pattern and degree of FDG uptake in cases of IVLBCL is partly explained by the findings reported by Shimada et al [17], who showed that diffuse infiltration of lymphoma cells in bone marrow specimens was associated with positive results of FDG-PET, whereas focal infiltration of a few lymphoma cells in bone marrow was associated with negative results of FDG-PET. They proposed that the number of tumor cells per volume might affect diagnostic accuracy of FDG-PET in IVLBCL. We also evaluated the tumor burden between intense-uptake lesions and lower-uptake lesions in the liver of this case, but the reason for variability in the degree of FDG uptake remains unknown. The disease activity of IVLBCL, the presence of subsequent tissue infarction caused by tumor cells, heterogeneity of hepatic fat distribution and inflammation [18], difference in blood glucose levels [19], and a dual blood supply may complexly affect FDG uptake in the liver in cases of IVLBCL. As mentioned above, lesions with multiple FDG uptake in PET/CT can suggest IVLBCL; however, the uptake can also be observed in other FDG-avid lymphoma and advanced cancers. Because strong suspicion of IVLBCL can help clinicians select less invasive procedures such as bone marrow and/or random skin biopsies for definitive diagnosis [10-12], further evaluation is warranted to distinguish IVLBCL from other FDG-avid tumors.

Our patient did not show any defects in the liver during the post-vascular phase of CEUS, and autopsy revealed diffuse infiltration of lymphoma cells and preserved Kupffer cells in
liver sinusoids. Emile et al showed that liver involvement in primary hepatic lymphoma is divided into 2 patterns: tumor-forming and diffuse infiltration [20]. Most lymphomas show tumor formation, while rare, aggressive lymphomas, including IVL BCL, hepatosplenic T-cell lymphoma, and aggressive NK-cell leukemia, show diffuse infiltration into liver sinusoids [1]. The use of Sonazoid CEUS in diagnosing tumor-forming lymphoma was reported by Kitahata et al [21], where 18 cases evaluated by CEUS showed various enhancement patterns in the vascular phase; all cases showed a defect during the post-vascular phase.

Figure 3. CEUS findings. (A) No nodular lesion is observed in B mode images of both liver lobes. (B) Before administration of Sonazoid. (C) Systemic enhancement is seen in the early vascular phase. (D) A defect is not observed at any locations in the post-vascular phase.
phase. As for the use of Sonazoid CEUS in diagnosing lymphoma with diffuse infiltration, Abe et al reported a case of IVLBCL evaluated by PET-CT and CEUS where multiple FDG-uptake lesions in the liver were observed, and corresponding to the lesions, hypoechoic areas were observed in the post-vascular phase [9], but no defects. They speculated that their results were due to accumulation of tumor cells. Our findings of CEUS agree with Abe et al regarding the absence of a defect. Our findings are in accord with the fact that lesions rich in Kupffer cells, including well-differentiated hepatocellular carcinoma (HCC) or focal nodular hyperplasia (FNH), do not show a defect in the post-vascular phase of CEUS [8,22]. In addition, our pathological findings are compatible with other case reports of IVLBCL in which tumor cells and Kupffer cells were both observed in liver sinusoids [23,24]. Our results suggest that, in combination with FDG-PET, CEUS can distinguish IVLBCL from mass-forming tumors by showing the absence of

Figure 4. Macroscopic findings of the liver show ill-defined, pale white changes in both liver lobes.

Figure 5. Histological findings of the liver show: (A) Diffuse infiltration of large neoplastic lymphoid cells in liver sinusoids. (HE staining); (B) The neoplastic cells positive for CD79a; (C) The neoplastic cells positive for CD20; (D) A number of CD68-positive Kupffer cells co-existent with the neoplastic cells in liver sinusoids.
Table 1. Cases of IVLBCL showing liver uptake on FDG-PET/CT [6,9,14-16].

<table>
<thead>
<tr>
<th>References</th>
<th>Age/Sex</th>
<th>Liver dysfunction</th>
<th>CT findings</th>
<th>FDG-PET/CT findings</th>
<th>CEUS findings</th>
<th>Biopsy site for diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiiba [6]</td>
<td>53/F</td>
<td>N.A.</td>
<td>Low density areas in liver and splenomegaly</td>
<td>Diffuse uptake in lungs and spleen, Multiple uptake lesions in liver</td>
<td>N.A.</td>
<td>Skin</td>
<td>Alive</td>
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<tr>
<td>Abe [9]</td>
<td>72/F</td>
<td>No</td>
<td>No findings</td>
<td>Multiple uptake lesions in liver</td>
<td>Hypoenhancement in post-vascular phase</td>
<td>Liver</td>
<td>Alive</td>
</tr>
<tr>
<td>Steen [14]</td>
<td>53/M</td>
<td>Yes</td>
<td>No findings</td>
<td>Diffuse uptake in liver</td>
<td>N.A.</td>
<td>Liver</td>
<td>Alive</td>
</tr>
<tr>
<td>Donald [15]</td>
<td>60/M</td>
<td>N.A.</td>
<td>Hepatosplenomegaly</td>
<td>Diffuse uptake in liver, spleen, bone marrow</td>
<td>N.A.</td>
<td>Bone marrow</td>
<td>N.A.</td>
</tr>
<tr>
<td>Li [16]</td>
<td>65/M</td>
<td>Yes</td>
<td>Low density areas in liver</td>
<td>Multiple uptake lesions in liver</td>
<td>N.A.</td>
<td>Liver</td>
<td>Alive</td>
</tr>
<tr>
<td>Current case</td>
<td>83/F</td>
<td>Yes</td>
<td>Low density areas in liver</td>
<td>Multiple uptake lesions in liver, bone marrow</td>
<td>Isoenhancement in post-vascular phase</td>
<td>Bone marrow</td>
<td>Died</td>
</tr>
</tbody>
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IVLBCl –intravascular large B-cell lymphoma; FDG-PET – fluorodeoxyglucose positron emission tomography; CT – computed tomography; CEUS – contrast-enhanced ultrasonography; F – Female; N.A. – not available; M – Male.

Conclusions

In summary, we experienced a case of IVLBCl that showed multiple FDG-uptake lesions in the liver, mimicking mass-forming lymphoma. CEUS did not detect any defects in the post-vascular phase, and autopsy revealed diffuse infiltration of lymphoma cells with preserved Kupffer cells in liver sinusoids. These results show that CEUS can distinguish IVLBCl from mass-forming lymphoma based on the absence of a defect in the post-vascular phase in a patient with clinically and radiographically suspected lymphoma involving the liver. This can assist clinicians to select appropriate lesions for biopsy. We believe our findings are novel and could contribute to the field of internal medicine and abdominal ultrasound. Further studies are required to validate the efficacy of CEUS in diagnosing IVLBCl and other rare lymphomas or diseases that show diffuse infiltration into liver sinusoids.

Department and Institution Where Work Was Done

Department of Hematology, Mishuku Hospital, Tokyo, Japan.

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References: