Abstract

Hepatic intravascular large B-cell lymphoma (IVL) is a rare disease entity that involves invasion into various organs. Due to the aggressive behavior and poor prognosis of the disease and the difficulty in making an early diagnosis, some cases are diagnosed at autopsy. Early suspicion and the use of imaging studies and liver biopsies are key for diagnosing IVL; however, no reports have described the results of imaging studies due to the limited number of cases. We herein report the results of imaging studies of hepatic IVL, including the findings PET-CT, dynamic-CT, EOB-MRI and CEUS. These results may help physicians to make an early diagnosis and improve the prognosis.

Key words: intravascular lymphoma, liver, imaging, contrast-enhanced ultrasonography, EOB-MRI

Introduction

Intravascular large B-cell lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL), as classified by the World Health Organization (1), characterized by the selective growth of lymphoma cells in the lumina of small vessels in various organs. Making an accurate diagnosis in the early stage of the disease is difficult because the symptoms, serum biochemical data and imaging findings differ without disease-specific characteristics. Furthermore, approximately 50% of cases have been reported to be diagnosed at autopsy (2). Therefore, the prognosis of IVL is poor, with a median survival of three months without chemotherapy (3). However, if chemotherapy is initiated at the early stage in patients with a good physical status, the 3-year overall survival rate reportedly increases to 33% following successful treatment (4), which is approximately similar to that of the total 5-year overall DLBCL survival rate of 30-50% (5). Therefore, making an early diagnosis of IVL in order to promptly initiate therapy is important, and obtaining a deeper understanding of the disease based on information obtained on imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US), is necessary.

We herein report, for the first time, a case that was successfully diagnosed using the aforementioned imaging studies and treated with R-CHOP therapy. Moreover, we review the literature and summarize the findings of these imaging studies in order to further understand IVL and make an early diagnosis of the disease. We believe that this information will help physicians to treat such cases.

Case Report

A 72-year-old woman was referred to our department

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with multiple areas of uptake of fluorine-18 fluorodeoxyglucose (FDG) in the liver on positron emission tomography-computed tomography (PET-CT) (Fig. 1a, b). The PET-CT study was performed to detect additional tumors because the patient had a spinal cord tumor at the L1 level with palsy of both lower extremities and bladder dysfunction (Fig. 1c). The spinal cord tumor also displayed a mild uptake of FDG on PET-CT. Moreover, she reported fatigue and loss of appetite, and the laboratory results showed an increase in the level of soluble interleukin-2 receptor (sIL-2R; 5,488 IU/mL). Other tumor markers, including the levels of carcinoembryonic antigen, carbohydrate antigen 19-9 and alpha-fetoprotein, were normal (Fig. 1d). Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI), dynamic contrast-enhanced CT and contrast-enhanced ultrasonography (CEUS) using a perfluorobutane microbubble agent (Sonazoid®, Daiichi Sankyo Co., Ltd., Tokyo, Japan) were performed to diagnose liver tumors (Fig. 2). EOB-MRI showed hypointensity lesions in the liver in the hepatobiliary phase consistent with the high-uptake lesions observed in the PET-CT study, suggesting the presence of liver tumors (a representative S7 lesion is shown in Fig. 2a). However, other wedge-shaped hypointensity lesions were not consistent with the high-uptake lesions observed on PET-CT (a representative S5-6 lesion is shown in Fig. 2b). No tumorous lesions were detected using dynamic CT (Fig. 2c); however, the latter lesions were clearly shown to have an uneven distribution of blood perfusion in the liver in the arterial phase (Fig. 2d). CEUS performed for the real-time observation of tumors and the hepatic blood flow showed low echoic areas in the Kupffer phase in the tumorous lesions (a representative S5-6 lesion is shown in Fig. 2e) with wedge-shaped low blood flow areas in the vascular arterial phase in the region consistent with the lesion shown in Fig. 2b, d (a representative S5-6 lesion is shown in Fig. 2f).

Based on the results of these imaging studies and the elevated sIL-2R levels, we suspected a diagnosis of hepatic intravascular lymphoma with multiple liver tumors invading the hepatic arteries. A liver biopsy of the tumorous area in the S7 lesion (Fig. 2a, c, e) and the wedge-shaped low blood flow area in the S5-6 lesion (Fig. 2b, d, f) was performed, followed by the histological diagnosis (Fig. 3). The tumorous S7 lesion showed accumulation of lymphoma cells in the sinusoids (Fig. 3a, b) that were positive for CD20 (Fig. 3c, d) and CD79a and negative for CD3 staining (data not shown). No tumor cells were found in the tissue collected from the wedge-shaped S5-6 lesion (Fig. 3e, f). In addition, no abnormal findings were noted in the bone marrow or cerebrospinal fluid.

The imaging findings and histological results of the tumorous lesions shown in Fig. 2a, e reflect the accumulation of tumor cells in the sinusoids, and the wedge-shaped low blood flow areas shown in Fig. 2b-f represent the tumor thrombi present in the hepatic artery on the proximal side (Fig. 1a; white arrow). Based on these findings, we diagnosed the patient with hepatic intravascular lymphoma invading both sinusoids, the hepatic arteries and spinal cord.

**Clinical course**

Eight courses of standard R-CHOP chemotherapy (com-
praising rituximab, doxorubicin, cyclophosphamide, vincristine and prednisone) were administered. The patient’s fatigue improved and her appetite recovered after the therapy. The sIL-2R level decreased to normal (353 IU/L); however, the palsies did not show any significant improvement. EOB-MRI, dynamic contrast-enhanced CT and CEUS demonstrated significant improvements in vascular invasion, and no tumorous or wedge-shaped lesions were observed (Fig. 4).

**Figure 2.** EOB-MRI, dynamic CT and CEUS of the liver before chemotherapy. (a, b) The hepatobiliary phase of EOB-MRI. (c, d) The arterial phase of dynamic CT. (e) The Kupffer phase of CEUS. (f) The vascular phase of CEUS (white dotted circles indicate wedge-shaped uneven perfusion in S5-6, and white arrowheads indicate the tumorous area in the S7 lesion).

**Figure 3.** Histological findings of the liver. Liver tissues were collected from the tumorous areas in the S7 lesion (a-d) and S5-6 lesion (e, f). Hematoxylin and Eosin staining (a, b, e, f). CD 20 staining (c, d) (a, c, e, 100×; b, d, f, 400×). The black bars represent 100 μm. The white arrows indicate lymphoma cells.
Careful analyses were performed using a time-intensity curve of the wedge-shaped low blood flow area in the S5-6 lesion in order to determine the effects of the tumor thrombus before and after the chemotherapy. The results showed an improvement in the low blood perfusion previously observed in the lesion and the uneven distribution indicated by the right blue and orange circles and lines in Fig. 5. In addition, importantly, PET-CT performed after the chemotherapy showed no abnormal uptake, and the spinal cord tumor had decrease in size on MRI (data not shown). These results suggest that the imaging studies were effective for the diagnosis and follow-up of the therapeutic effects on hepatic IVL. No tumor recurrence has been noted for seven months after the therapy.

**Discussion**

IVL is a rare subtype of extranodal DLBCL characterized by aggressive behavior due to the proliferation of lymphoma cells in the lumen of small- to medium-sized vessels. The symptoms vary [fever, 45%; cutaneous symptoms, 39%; manifestations in the central nervous system, 34%; pain, 21%; fatigue, 16%; and weight loss, 11% (6)] as a result of invasion into the vessels of various organs (7-9). Two variants of IVL have been reported: 1) the Classical variant

![Figure 4.](image)

**Figure 4.** EOB-MRI, dynamic CT and CEUS of the liver after chemotherapy. (a, b) The hepatobiliary phase of EOB-MRI. (c, d) The arterial phase of dynamic CT study. (e) The Kupffer phase of CEUS. (f) The vascular phase of CEUS (white dotted circles indicate wedge-shaped uneven perfusion in S5-6, and white arrowheads indicate the tumorous area in the S7 lesion).

![Figure 5.](image)

**Figure 5.** Time intensity curve of the CEUS findings. Time intensity curve of the real-time dynamic flow in the S5-6 lesion before (a) and after (b) chemotherapy. The yellow, red and green circles in the left panel and the lines in the right panel indicate the areas and changes in intensity on CEUS in the lesions with normal blood perfusion. The light blue and orange circles indicate the area in the left panel and the lines in the right panel indicate the lesions with decreased and uneven blood perfusion.
The challenge is, however, to suspect the disease based on symptoms. The levels of tumor markers, such as sIL-2R, and the findings of noninvasive methods, such as FDG-PET, US, CT, MRI and so on. A strong suspicion should be followed up with a biopsy during the antemortem period because the number of cases involving the liver diagnosed in the antemortem period is lower than that observed in the postmortem period (12-21) (Table). Our literature review of hepatic IVL cases diagnosed using imaging studies of the liver revealed that six of 10 cases were diagnosed at autopsy, and no specific findings were observed in the conventional CT studies (Table). However, all four patients who underwent a liver biopsy exhibited hepatosplenic failure on CT and, importantly, three of these patients survived after chemotherapy (no information was obtained in case 1). These results suggest that conducting imaging studies of the liver can be helpful for making an earlier diagnosis.

Recently, multiple imaging modalities have been developed for the diagnosis of liver tumors, including CT, MRI and US. More recently, Gd-EOB-DTPA contrast medium for use in MRI (22) and a perflubutane microbubble agent (Sonazoid) for use in US (23) have been approved for the diagnosis of liver tumors, being absorbed by hepatocytes and Kupffer cells in sinusoids, respectively. Dynamic studies using these agents are helpful for determining the characteristics of liver tumors (e.g., origin, invasive growth into vessels). Few reports have discussed such findings for IVL due to the limited number of cases (Table). Our literature review showed that only one of 10 patients was examined using PET-CT and dynamic CT and that EOB-MRI and CEUS were not performed in any case (Table). The imaging find-
ings reported in the present case will help to detect uneven blood perfusion due to vessel invasion and the presence of tumorous lesions, followed by the use of liver biopsies at an earlier stage in order to immediately administer chemotherapy. Our case demonstrated two patterns in the imaging studies: tumorous lesions and wedge-shaped uneven low blood flow lesions. The former lesions exhibited invasion of DLBCL cells into the sinusoids, while the latter showed tumor-based thrombotic effects on the more proximal side of the hepatic artery. As expected, no tumor cells were seen in this area. Similar findings were reported by Yasuda et al. (16), who described multiple thrombotic lesions in the hepatic vessels and splenic vein at autopsy; these lesions were seen on the CT studies performed in the antemortem period and confirmed in the postmortem period. These findings suggest that, if a diagnosis of hepatic IVL is suspected when employing multiple imaging modalities, a tumor lesion-specific liver biopsy should be performed to confirm the presence of sinusoidal invasion, because a random liver biopsy may fail to detect tumor cells if it is performed in peripheral lesions (as evidenced in our case).

In summary, we herein reported the case of a patient successfully diagnosed with IVL based on the sIL-2R level, various imaging modality findings and the results of a lesion-specific liver biopsy who was treated with R-CHOP therapy. Our results suggest that PET-CT is useful for detecting the accumulation of lesions, while dynamic CT, EOB-MRI and CEUS are helpful for identifying lesions for a biopsy. These findings and the literature review provide important information regarding IVL and its mechanisms for planning successful therapy.

Conclusion

IVL is a rare disease with a poor prognosis that is difficult to diagnose in the early stage. However, we herein reported a case of IVL that was successfully diagnosed using various imaging studies and a tumor-targeted liver biopsy. In addition, with the development of various imaging modalities and contrast agents, the minute findings of hepatic IVL observed on imaging studies and the results of our literature review will be helpful for diagnosing the disease at the early phase and improving the prognosis.

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

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References

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