Case Reports in Oncology

Case Rep Oncol 2015;8:50–57

DOI: 10.1159/000375118
Published online: February 3, 2015

1662–6575/15/0081–0050$39.50/0
www.karger.com/cro

A Case of Contiguous Primary Hepatic Marginal Zone B-Cell Lymphoma and Hemangioma Ultimately Diagnosed Using Contrast-Enhanced Ultrasonography

Kazue Shiozawa[a] Manabu Watanabe[a] Takashi Ikehara[a]
Yasushi Matsukiyo[a] Yoshinori Kikuchi[a] Hironori Kaneko[b]
Yoichiro Okubo[c] Kazutoshi Shibuya[c] Yoshinori Igarashi[a]
Yasukiyo Sumino[a]

[a]Division of Gastroenterology and Hepatology, Department of Internal Medicine, [b]Division of Gastroenterological Surgery, and [c]Department of Surgical Pathology, Toho University Medical Center, Omori Hospital, Tokyo, Japan

Key Words
Primary hepatic malignant lymphoma · Malignant lymphoma of mucosa-associated lymphoid tissue · Hemangioma · Contrast-enhanced ultrasonography

Abstract
Primary hepatic marginal zone B-cell malignant lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is extremely rare. We present a case in which a lesion was diagnosed as 2 contiguous tumors (MALT lymphoma and hemangioma) using contrast-enhanced ultrasonography (US) with sonazoid. There has been no previous case of contiguous hepatic MALT lymphoma and hemangioma. The present case was a female with no medical history. We detected a snowman-like appearance, which was a tumor of 15 mm in diameter with hypo- and hyper-echogenicities in the lateral and medial parts, respectively, in the Couinaud's segment (S6) of the liver on US. The tumor appeared as a single lesion with a low-density area in the unenhanced phase and prolonged enhancement in the equilibrium phases on dynamic CT. On MRI, the whole lesion showed a low-intensity signal on T1-weighted imaging, but isointensity in the lateral part and high intensity in the medial part were seen on T2-weighted imaging. On contrast-enhanced US, the lateral hypoechoic region

Manabu Watanabe
Division of Gastroenterology and Hepatology, Department of Internal Medicine
Toho University Medical Center, Omori Hospital, 6-11-1 Omorinishi
Ota-ku, Tokyo 143-8541 (Japan)
E-Mail manabu62@med.toho-u.ac.jp

was homogenously hyperenhanced in the early vascular phase, and the contrast medium was washed out after about 30 s; in contrast, the medial hyperechoic region was gradually stained from the margin toward the central region. The tumor showed a defect in both hypo- and hyperechoic regions in the postvascular phase. Hemangioma was suspected for the medial part based on the typical image findings, but the lateral part was not given a diagnosis. Thus, surgical resection was performed. The medial part was a hemangioma, and the lateral part was a MALT lymphoma by histopathological findings.

Introduction

Marginal zone B-cell malignant lymphoma is a low-grade malignant non-Hodgkin's lymphoma that develops in mucosa-associated lymphoid tissue (MALT) [1]. This disease frequently develops in the stomach and also occurs in the salivary gland, thyroid, and lung. In contrast, primary hepatic malignant lymphoma is rare. Most cases are diffuse large B-cell lymphoma, and the incidence of hepatic MALT lymphoma is low among cases of primary hepatic malignant lymphoma [2–5]. Here, we describe a rare case in which a lesion was initially thought to be a single tumor but was ultimately diagnosed as 2 contiguous tumors (MALT lymphoma and hemangioma) using contrast-enhanced ultrasonography (CEUS) with sonazoid (Daiichi Sankyo, Tokyo, Japan). There has been no previous case of contiguous hepatic MALT lymphoma and hemangioma. We report the case with a literature review.

Case Report

The patient was a 60-year-old female in whom a tumor of 15 mm in diameter was detected in the Couinaud's segment (S6) of the liver on the grayscale US in a medical examination. She visited our hospital for further examination and treatment. She had no subjective symptoms, relevant medical or family history, and did not drink alcohol. Physical findings on admission were: blood pressure 136/80 mm Hg, pulse rate 80/min, and body temperature 36.4°C. Blood tests on admission showed Hb 10.4 g/dl (normal 14.0–17.0 g/dl), suggesting a mild anemia. Tumor markers were normal, tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) were negative, and there were no other abnormal findings.

Grayscale US showed a tumor with a snowman-like appearance and a relatively clear boundary in the S6 of the liver, with hypo- and hyperechoic areas in the lateral and medial parts of the lesion, respectively (fig. 1a). On dynamic CT, the tumor was shown as a single lesion protruding from the S6. The tumor had a pale, low-density area on unenhanced CT, and prolonged enhancement in the equilibrium phases (fig. 1b). On MRI, the whole lesion gave a low-intensity signal on T1-weighted imaging, but isointensity in the lateral part and high intensity in the medial part were seen on T2-weighted imaging. Similarly, the lateral part showed high intensity and the medial part had a higher intensity on heavy T2-weighted imaging (fig. 1c). On dynamic MRI, the lateral part was enhanced in the arterial phase, and enhancement persisted in the portal phase. In contrast, the medial part was gradually enhanced in the arterial phase, compared to the portal phase.

CEUS was performed using an Aplio XG (Toshiba Medical Systems, Tokyo, Japan) with a convex probe (PVT-375BT, 3.75 MHz frequency). The mechanical index for the acoustic output was set to 0.2, and a single focus point was set at the lower margin of the lesion. Sonazoid (0.5 ml) was injected into the left cubital vein followed by a flushing with 10 ml of nor-

mal saline. The lateral hypoechoic region was homogenously hyperenhanced in the vascular phase (0–40 s) early after injection, and the contrast medium was washed out after about 30 s. The medial hyperechoic region was gradually stained from the margin toward the central region (fig. 2). The tumor showed a defect in both hypo- and hyperechoic regions in the postvascular phase (after 15 min). Similar findings were observed after a second intravenous injection of 0.5 ml of sonazoid using defect reperfusion imaging [6] in the postvascular phase. The imaging findings suggested that 2 contiguous tumors were present. Liver hemangioma was suspected for the medial part of the lesion based on the typical contrast findings on MRI and CEUS. In the lateral part, the contrast medium was washed out in the vascular phase on CEUS early after the intravenous injection of sonazoid. Furthermore, the lateral part showed a defect in the postvascular phase, and this defect led to the suspicion of a malignant tumor, including hepatocellular carcinoma (HCC). Thus, surgical resection was performed.

In a macroscopic examination of the resected specimen, the medial part was whitish and the lateral part was yellowish-white. On hematoxylin and eosin (HE) staining, the medial part comprised blood vessels formed by a single layer of flattened endothelial cells and an interstitium formed by thin connective tissue, with the vascular lumen filled with blood. Based on these findings, the medial part of the tumor was diagnosed as hemangioma. In the lateral part, lymphocyte infiltration in a dense arrangement was observed on HE staining, and most lymphocytes contained a moderately sized nucleus, but some cells contained a large nucleus and noticeable nucleolus (fig. 3a). On immunohistochemical staining, CD30-expressing lymphocytes containing a large nucleus were occasionally noted. B lymphocytes expressing CD20 and CD79α were present (fig. 3b, c), but bcl-2 expression in the germinal center was unclear. Lymphocytes expressing CD43 were more common than those expressing CD3. Similar findings were present in the germinal center, with atypical lymphocytes invading the germinal center. Based on these findings, the lateral part of the tumor was diagnosed as marginal zone B-cell lymphoma. The patient was discharged 5 days after surgery.

Discussion

Isaacson and Wright [7] first proposed the name of MALT lymphoma for extranodal malignant lymphoma of marginal zone B-cell origin in 1983. MALT lymphoma is a low-grade malignant non-Hodgkin's lymphoma that develops in mucosa-associated lymphoid tissue, and accounts for 7–8% of all cases. MALT lymphoma frequently develops in the stomach, and also occurs in the salivary gland, thyroid, and lung [7]. Primary hepatic malignant lymphoma is rare, with most cases being diffuse large B-cell lymphoma and less than 10% being MALT lymphoma [2–5].

Many cases of MALT lymphoma are solitary, imaging findings are diverse, and it is difficult to make a definite diagnosis based on imaging alone. Exclusion of HCC may not be possible and a definite diagnosis can only be made histopathologically after surgical resection in many cases [8–10]. In our patient, the lesion was initially considered to be a single tumor, but imaging findings indicated that it had 2 distinct regions. The presence of contiguous MALT lymphoma and hemangioma was confirmed histopathologically. A literature search indicated that 2 cases of simultaneous MALT lymphoma and hemangioma in the liver have been reported, with focal nodular hyperplasia also present in 1 of these cases [11, 12]. In both previous cases, MALT lymphoma and hemangioma were separate, and thus there has been no previous case in which the tumors initially appeared to be a single tumor. In our

patient, MALT lymphoma and hemangioma were in contact, but each tumor was independent, rather than pathologically continuous, on histopathological examination. The causal relationship between the tumors was unclear. Concomitant MALT lymphoma and hemangioma were considered to have no causal relationship in the 2 previous cases [11, 12].

The characteristic imaging findings of hepatic MALT lymphoma are nonspecific, but include a relatively hypoechoic mass without a clear hypoechoic margin on grayscale US, hypoenhancement of the tumor in the arterial phase on dynamic CT, and low and high intensities on T1- and T2-weighted images on MRI, respectively [13]. In CEUS using Sono View (Bracco, Milan, Italy) in 2 patients with hepatic primary MALT lymphoma, Foschi et al. [14] found that the lesions were inhomogeneously hyperenhanced in the arterial phase and hypoenhanced in the portal and late phases. These 2 patients were HBV-positive: one was an HBV-inactive carrier, and the other had chronic HBV hepatitis. Dynamic CT in both patients showed a slight hyperenhancement in the arterial phase, and hypoenhancement in the portal phases, and HCC was suspected. It was difficult to make a preoperative diagnosis, and the tumor was finally diagnosed histopathologically as hepatic MALT lymphoma.

The development of a MALT lymphoma is thought to involve persistent chronic inflammation, and *Helicobacter pylori* infection is well-known in gastric MALT lymphoma. In primary hepatic MALT lymphoma, chronic liver disorders such as HBV- or HCV-associated chronic hepatitis, hepatic cirrhosis, and primary biliary cirrhosis are occasionally found in the background liver [15]. Our patient was negative for viruses and the background liver was normal, but homogenous hyperenhancement was observed in the vascular phase early after sonazoid injection, and the contrast medium was washed out after about 30 s on CEUS. A defect was also noted in the postvascular phase, based on which the possibility of a malignant tumor, including HCC, could not be ruled out. However, the presence of 2 contiguous tumors was indicated by real-time evaluation hemodynamics in the tumor using CEUS, which indicates the utility of CEUS for a proper diagnosis.

Tumor penetration by existing blood vessels on dynamic CT and MRI is a characteristic finding in hepatic malignant lymphoma [8, 10]. However, in our case, no blood vessel penetrating the tumor was evident in any imaging. This feature may not have been visualizable in our case, or the absence of blood vessels penetrating the tumor may differentiate primary hepatic MALT lymphoma from other malignant lymphomas. Only a few reported cases of primary hepatic MALT lymphoma have included CEUS findings, and no typical enhancement pattern on CEUS has been established. The presence of blood vessels penetrating the tumor is useful for the diagnosis of malignant lymphoma, and CEUS evaluation of intratumoral hemodynamics in real time may be more likely to visualize penetrating blood vessels, compared to dynamic CT and MRI. It is possible that the absence of this feature differentiates primary hepatic MALT lymphoma from other malignant lymphomas. Confirmation of this possibility will require further evidence from CEUS evaluation of more cases of primary hepatic MALT lymphoma.

Conclusion

MALT lymphoma is rare among primary hepatic malignant lymphomas. The lesion in our patient was initially considered to be a single tumor, but contiguous hepatic MALT lymphoma and hemangioma were actually present. The concomitant occurrence of these tumors is rare, and no cases with 2 tumors in contact have been previously reported. The tumors

gave different enhancement patterns on CEUS and their presence was confirmed histopathologically, based on which we were able to make the final diagnosis.

Acknowledgements

The authors would like to thank Kenichi Maruyama and the staff of the Department of Clinical Functional Physiology, Toho University Medical Center, Omori Hospital.

References

1 Isaacson PG, Banks PM, Best PV, McLure SP, Muller-Hermelink HK, Wyatt JI: Primary low-grade hepatic B-cell lymphoma of mucosaassociated lymphoid tissue (MALT)-type. Am J Surg Pathol 1995;19:571–575.
2 Lei KI: Primary non-Hodgkin's lymphoma of the liver. Leuk Lymphoma 1998;29:293–299.
3 Zucca E, Conconi A, Pedrinis E, Cortelazzo S, Motta T, Gospodarowicz MK, Patterson BJ, Ferreri AJ, Ponzoni M, Devizzi L, Giardini R, Pinotti G, Capella C, Zinzani PL, Pileri S, López-Guillermo A, Campo E, Ambrosetti A, Baldini L, Cavalli F; International Extranodal Lymphoma Study Group: Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003;101:2489–2495.
4 Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252–260.
5 Bronowicki JP, Bineau C, Feugier P, Hermine O, Brousse N, Oberti F, Rousselet MC, Dharancy S, Gaulard P, Flejou JF, Cazals-Hatem D, Labouyrie E: Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. Hepatology 2003;37:781–787.
6 Kudo M, Hatanaka K, Maekawa K: Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using Sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78:40–45.
7 Isaacson P, Wright DH: Malignant lymphoma of mucosa associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 1983;52:1410–1416.
8 Fukuya T, Honda H, Murata S, Yasumori K, Hayashi T, Ishibashi H, Matsumata T, Masuda K: MRI of primary lymphoma of the liver. J Comput Assist Tomogr 1993;17:596–598.
9 Weissleder R, Stark DD, Elizondo G, Hahn PF, Compton C, Saini S, Wittenberg J, Ferrucci JT: MRI of hepatic lymphoma. Magn Reson Imaging 1988;6:675–681.
10 Apicella PL, Mirowitz SA, Weinreb JC: Extension of vessels through hepatic neoplasms: MR and CT findings. Radiology 1994;191:135–136.
11 Nagano K, Fukuda Y, Nakano I, Katano Y, Toyoda H, Nonami T, Nagasaka T, Hayakawa T: Reactive lymphoid hyperplasia of liver coexisting with chronic thyroiditis: radiographical characteristics of the disorder. J Gastroenterol Hepatol 1999;14:163–167.
12 Willenbrock K, Kriener S, Oeschger S, Hansmann ML: Nodular lymphoid lesion of the liver with simultaneous focal nodular hyperplasia and hemangioma: discrimination from primary hepatic MALT-type non-Hodgkin's lymphoma. Virchows Arch 2006;448:223–227.
13 Masood A, Kairouz S, Hudhud KH, Hegazi AZ, Banu A, Gupta NC: Primary non-Hodgkin's lymphoma of the liver. Curr Oncol 2009;16:74–77.
14 Foschi FG, Dall'Aglio AC, Marano G, Lanzi A, Savini P, Piscaglia F, Serra C, Cursaro C, Bernardi M, Andreone P, Stefanini GF: Role of contrast-enhanced ultrasonography in primary hepatic lymphoma. J Ultrasound Med 2010;29:1353–1356.
15 Murakami J, Fukushima N, Ueno H, Saito T, Watanabe T, Tanosaki R, Kobayashi Y, Matsuno Y, Tobinai K: Primary hepatic low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue type: a case report and review of the literature. Int J Hematol 2002;75:85–90.

Case Rep Oncol 2015;8:50–57
DOI: 10.1159/000375118

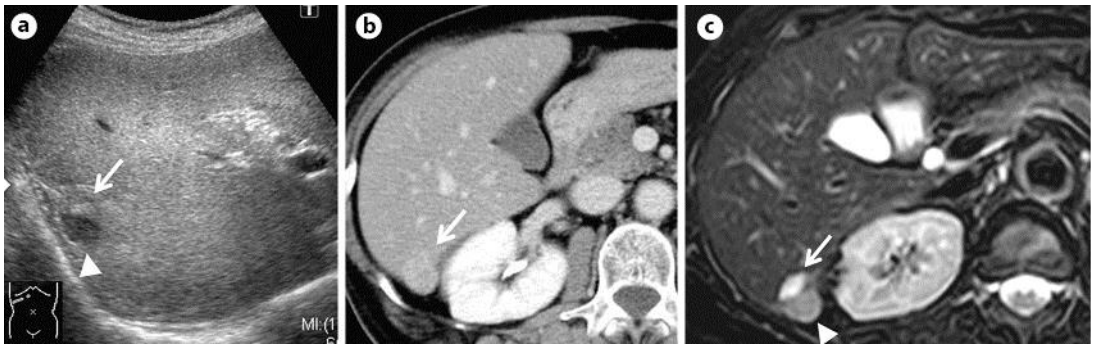

Fig. 1. Grayscale US showed a tumor with a snowman-like appearance and a relatively clear boundary in the S6 of the liver, with hypo- and hyperechoic areas in the lateral (arrowhead) and medial parts (arrow) of the lesion, respectively (**a**). Contrast-enhanced CT showed a tumor prolonged enhancement in the equilibrium phases (arrow) (**b**). MRI showed high intensity in the lateral part of the tumor (arrowhead) and higher intensity in the medial part of the tumor (arrow) on heavy T2-weighted imaging (**c**).

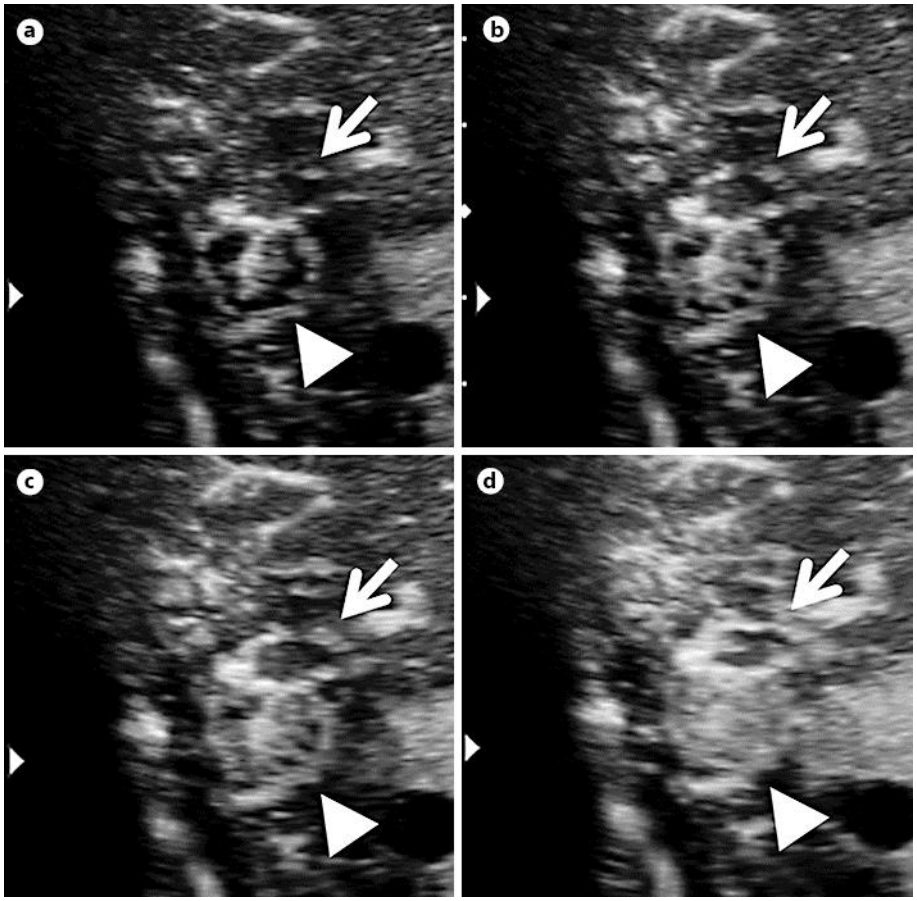

Fig. 2. The lateral part of the lesion showed homogenous hyperenhancement (arrowhead) and the medial part of the lesion showed gradually stained from the margin toward the central region (arrow) in the vascular phase on contrast-enhanced US (16 s (**a**), 18 s (**b**), 20 s (**c**), 22 s (**d**) after injection).

Case Rep Oncol 2015;8:50–57
DOI: 10.1159/000375118

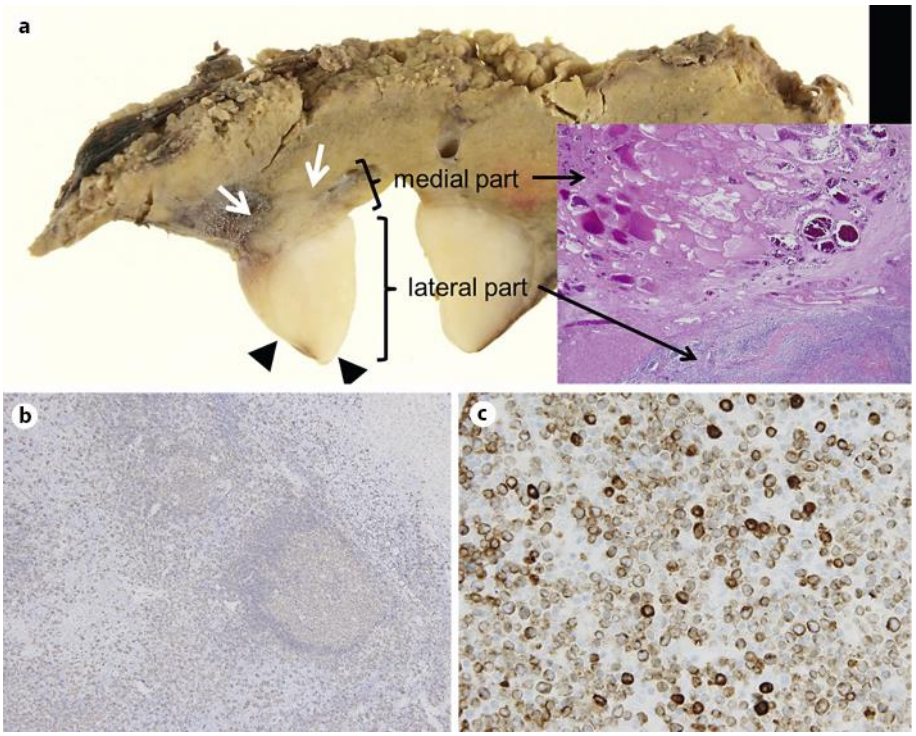

Fig. 3. A cut section of the resected liver showed a whitish nodular lesion in the medial part (white arrow) and a yellowish-white nodular lesion in the lateral part (black arrowhead) (**a**). The medial part comprised blood vessels formed by a single layer of flattened endothelial cells and an interstitium formed by thin connective tissue. In the lateral part, lymphocyte infiltration in a dense arrangement was observed (**a**; HE, ×40). On immunohistochemical staining, B lymphocytes expressing CD20 (**b**; CD20, ×100) and CD79α (**c**; CD79α, ×400) were present.