A Surgical Case of Primary Splenic Malignant Lymphoma Complicating Chronic Hepatitis C

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The patient was a 70-year-old man. Hepatic dysfunction was found in 1988 and chronic hepatitis C was diagnosed in 1993. He received interferon-alpha therapy, but did not respond to it. Thereafter, he was treated with ursodeoxycholic acid. In September 2010, abdominal ultrasound showed a hypoechoic tumor (29 x 25 mm) in the lower pole of the spleen, and this lesion became larger one year later (74 x 66 x 71 mm). Abdominal CT revealed a hypovascular heterogeneous tumor with smooth margins on both dynamic and delayed phase scans. MRI displayed a tumor with a low signal intensity on T2WI. Abdominal angiography confirmed that the lesion was hypovascular. 67Ga scintigraphy showed abnormal accumulation confined to the spleen. Bone marrow biopsy did not reveal any abnormalities. Based on these findings, primary splenic malignant lymphoma (PSML) complicating chronic hepatitis C was diagnosed and splenectomy was performed. A tumor (78 x 60 mm) was found in the lower pole of the resected spleen and pathologic examination revealed diffuse large B cell lymphoma (DLBCL). Four courses of postoperative R-CHOP therapy were performed. At present, he continues to use ursodeoxycholic acid with no recurrence after four years. In conclusion, we report our experience of a patient who had PSML complicating chronic hepatitis C with discussion of the literature.

Key words: Primary splenic malignant lymphoma, hepatitis C, diffuse large B cell lymphoma

INTRODUCTION

Splenic tumors (both primary and secondary) are rare [1, 2], being metastatic tumors, malignant lymphoma, and hemangioma in descending order of frequency, and making a correct preoperative diagnosis is difficult. Gordon *et al*. reported that malignant lymphoma accounted for a high proportion of primary splenic malignant neoplasms (22.2%) [3]. Primary splenic malignant lymphoma (PSML) is considered to be one of the complications that occurs in patients with chronic hepatitis C [4]. Here we report our experience with a patient who underwent resection of PSML detected during treatment of chronic hepatitis C, as well as discussing the relevant literature.

CASE REPORT

This report was approved by the ethics committee of Tokai University Tokyo Hospital (Tokyo, Japan) and the patient provided written informed consent in accordance with the requirements of the hospital institutional review board. The patient was a 70-year-old man. In 1988, hepatic dysfunction was detected. In 1993, active chronic hepatitis associated with HCV infection was diagnosed from the results of detailed investigation including liver biopsy. HCV-RNA was 10^9 log IU/ml and the viral genotype was IB. Treatment with interferon-alpha was performed for six months. Although HCV-RNA decreased to 10^2 log IU/ml after three months, the treatment was ultimately ineffective and a response was not obtained. Thereafter, he was treated with ursodeoxycholic acid and followed. In September 2010, routine abdominal ultrasound showed a hypoechoic tumor (29 x 25 mm) in the lower pole of the spleen (Fig. 1A). There were no associated physical findings. He was considered to have a benign lesion such as hemangioma or lymphangioma and follow-up was continued. Approximately one year later, abdominal ultrasonography showed enlargement of the splenic tumor (74 x 66 x 71 mm), which had well-defined borders, heterogeneous internal echogenicity, and posterior echo enhancement (Fig. 1B). Contrast-enhanced abdominal CT revealed a poorly enhanced tumor (73 x 63 mm) with well-defined and smooth margins in the lower pole of the spleen (Fig. 2). Abdominal MRI displayed a tumor (about 6 x 9 cm) with faint heterogeneous low signal intensity and well-defined borders on T2-weighted images (Fig. 3). On diffusion-weighted images and apparent diffusion coefficient (ADC) maps, the lesion had a lower signal intensity in comparison to the surrounding splenic parenchyma. Abdominal angiography detected a hypovascular tumor (about 7 cm in

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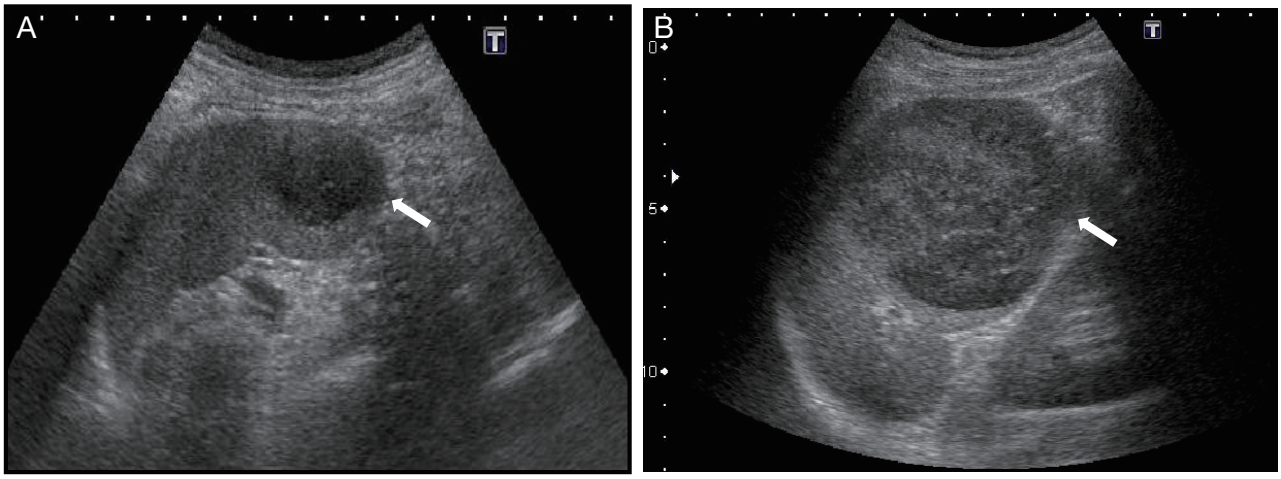

Fig. 1 Ultrasound findings:
(A) A hypoechoic tumor (29 x 25 mm) is seen in the lower pole of the spleen in 2010.
(B) Enlargement of the tumor (74 x 66 x 71 mm) is evident in 2011.

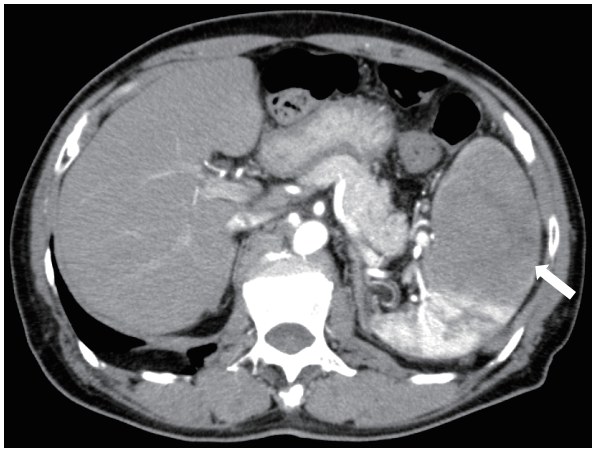

Fig. 2 CT findings:
There is a poorly enhanced tumor with well-defined and smooth margins in the lower pole of the spleen (arrow).

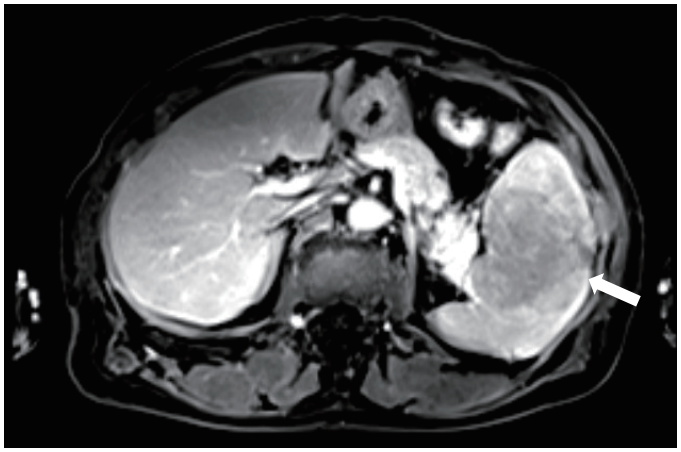

Fig. 3 MRI findings:
There is a tumor (about 6 x 9 cm) showing faint heterogeneous low signal intensity with well-defined borders.

diameter) in the lower pole of the spleen (Fig. 4). ^{67}Ga scintigraphy showed strong abnormal accumulation that was confined to the spleen (Fig. 5). Laboratory tests revealed slight elevation of total bilirubin (1.6 mg/dl) and LDH (650 IU/L), while soluble IL-2 receptor antibody was within the normal range (385 U/ml). Bone marrow examination was normal. Based on the above findings, PSML associated with chronic hepatitis C was diagnosed. He underwent splenectomy and perisplenic lymph node dissection. At laparotomy, the liver displayed mild hypertrophy and a dull edge with evidence of chronic hepatitis, but ascites, ventral circulation, and intraabdominal lymphadenopathy were not observed. Resected perisplenic lymph nodes were submitted for rapid intraoperative pathological examination, which was negative. The spleen measured 140 x 100 x 55 mm and weighed about 500 g. The tumor (78 x 60 mm) was a pale yellow solid mass that showed a well-defined border with the surrounding splenic parenchyma (Fig. 6).

Histopathological examination showed that the tumor was composed of diffusely proliferating atypical cells with irregular medium to large round or oval nuclei and a high N/C ratio (Fig. 7). Immunohistological examination yielded the following results: CD5(+), CD20(L26)(+), CD79a(+), MUMI(+), Bcl-2(+, 80%), Bcl-6(+,70%), c-myc(-/+)(20%), MIB-I80%CD3(-), CD10(-), CD30(ki-1)(-), CD43(-), ALK-1(-), CKAE1/AE3(-), TdT(-), cyclinD1(-), and EBV-ISH(-) (Fig. 8). Because analysis of sections of the entire specimen revealed no low grade lymphoma outside the tumor, de novo diffuse large B cell lymphoma (DLBCL) was diagnosed. Postoperatively, he was given four courses of R-CHOP therapy. At present, he continues to take ursodeoxycholic acid and there have been no signs of recurrence after four years.

DISCUSSION

The spleen is the largest organ in the reticuloendothelial system. Splenic malignancies are uncommon, accounting for only 0.0087–0.64% of all malignant tumors [1, 2]. Malignant lymphoma is the most frequent type of primary splenic malignant tumor, and is reported to account for 22.2–77.8% of splenic malignancies [3, 4]. Because the spleen is frequently involved by malignant lymphoma arising elsewhere, it is often

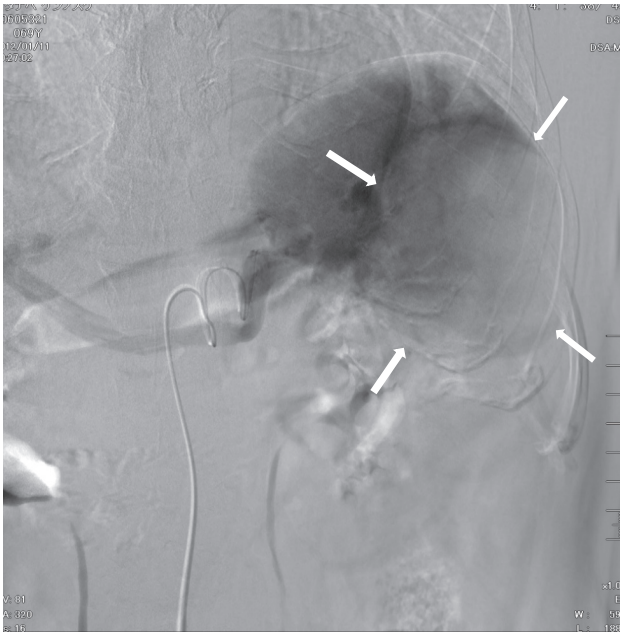

Fig. 4 Abdominal angiography:
A hypovascular round area (about 7 cm in diameter) with marginal enhancement is seen in the lower pole of the spleen.

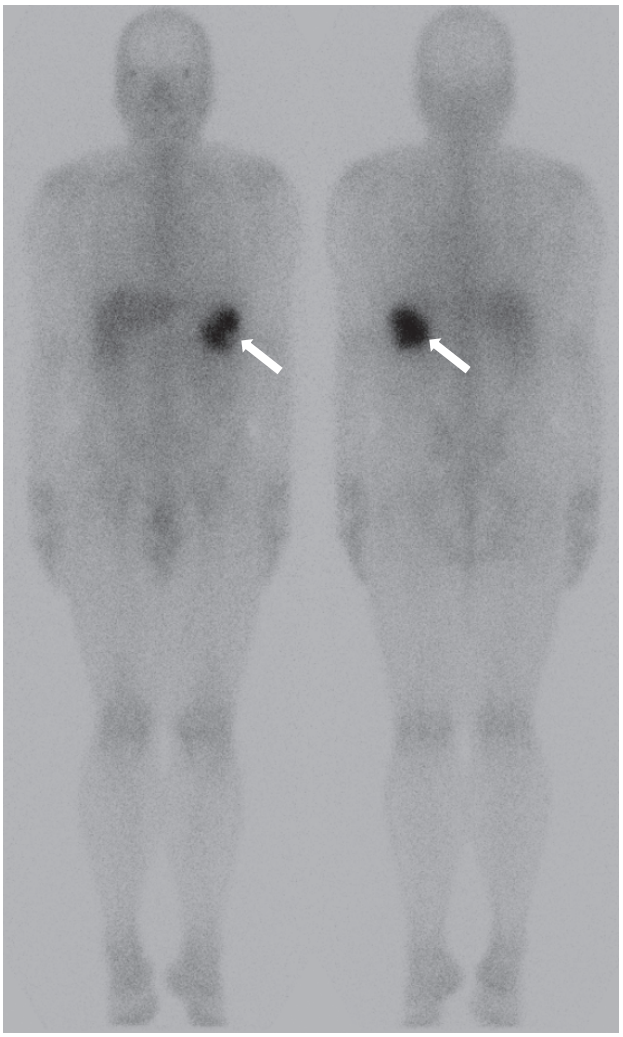

Fig. 5 ^{67}Ga scintigraphy:
There is marked accumulation in the spleen.

difficult to determine whether the tumor is primary or not. Diagnostic criteria for PSML have been proposed by Gupta [5], Spier [6], and Ahmann [7]. The present patient had no abdominal findings based on Gupta's criteria, but fulfilled the criteria of Ahmann and Spier, so PSML was diagnosed. Based on pathologic examination, Yata *et al*. reported that NHL accounted for 98% of PSML, among which DLBCL comprised 65% (the highest) and 98% of these tumors were B-cell lymphoma [8]. With respect to the relationship between malignant lymphoma and HCV infection, Ferri *et al*. reported in 1994 that 30% of malignant lymphoma patients were positive for HCV antibody and 32% had HCV viremia [4]. Subsequently, there were multiple reports of a significantly high HCV infection rate in patients with malignant lymphoma [9, 10]. In Japan, Hijioka *et al*. reported that 77.3% of PSML patients were positive for HCV antibody [11]. It was reported that monocytes and lymphocytes are directly infected by hepatitis C virus, which may lead to the development of lymphoproliferative diseases [12].

A search of the Japan Medical Abstracts Society website using the keywords "hepatitis C" and "splenic malignant lymphoma" detected eight cases of PSML associated with chronic hepatitis C between 1995 and 2015, for which details of the blood transfusion history were described (including reports in conference proceedings). The male-to-female ratio was 3 : 1. Blood transfusion, the possible cause of HCV infection, was performed during surgery in 6 patients, but the timing of transfusion was unknown in 2 patients. The mean and median age was 62.45 years and 64 (range: 55–75) years, respectively, while the mean and median time from blood transfusion to detection of the tumor was 34 and 34.5 (23–40) years, respectively.

Morel *et al*. compared patients with and without splenectomy and reported that the 50% survival time was 108 and 24 months, respectively, showing a significant difference [13]. Bairey *et al*. described that splenectomy at diagnosis was associated with longer PFS, and splenectomy at diagnosis and rituximab treatment were negative for OS [14]. If a tumor is localized, performance of splenectomy including splenic hilar lymph node dissection can be recommended. The diagnosis is established by examination of the resected specimen, and postoperative chemotherapy or radiotherapy is selected. In the present patient, histopathologic examination showed no low grade lymphoma in the spleen, so de novo DLBCL was diagnosed and he was given four courses of R-CHOP therapy [15].

When a splenic tumor is detected in a patient with chronic hepatitis C like the present case, follow-up by diagnostic imaging should be performed at relatively short intervals keeping the possibility of lymphoma in mind.

In recent years, with advances in the treatment of chronic hepatitis C, the number of long-term survivors has increased. Accordingly, more attention should be paid to the risk of lymphoma in these patients because of an increase in survivors for 30 years or more.

CONCLUSION

We reported our experience with a patient who underwent resection of PSML that was detected during

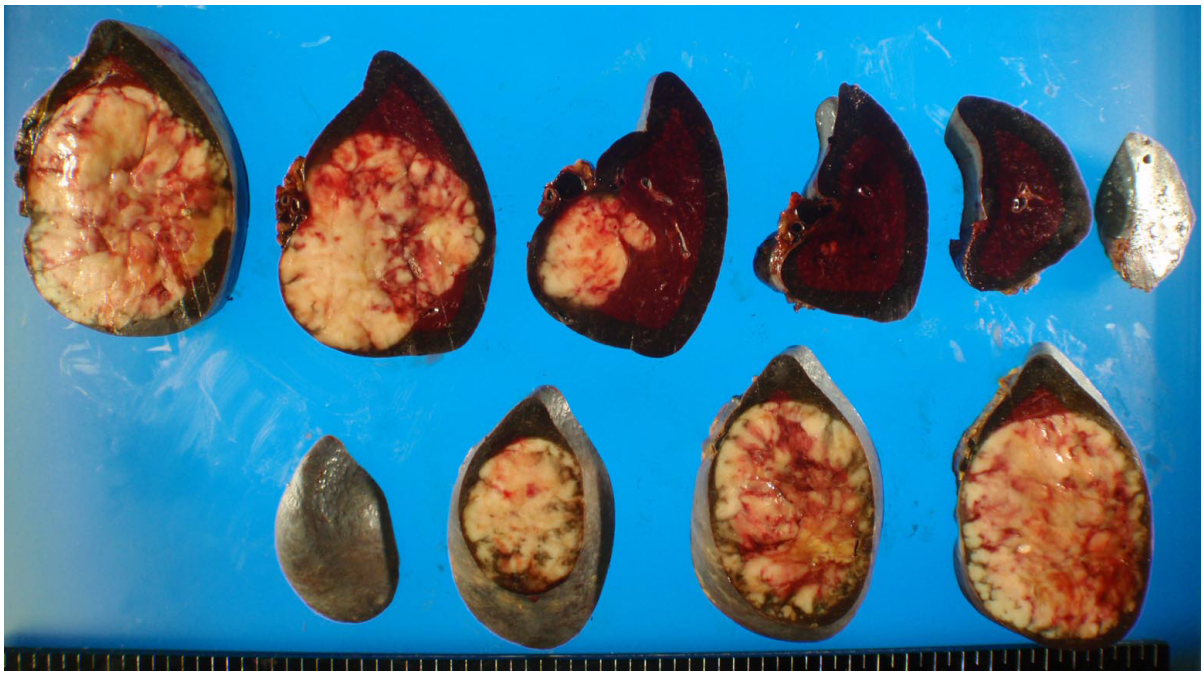

Fig. 6 Findings of the resected specimen:
The lesion is a solid tumor (78 x 60 mm) that has a well-defined border with the normal spleen and a pale yellow cut surface.

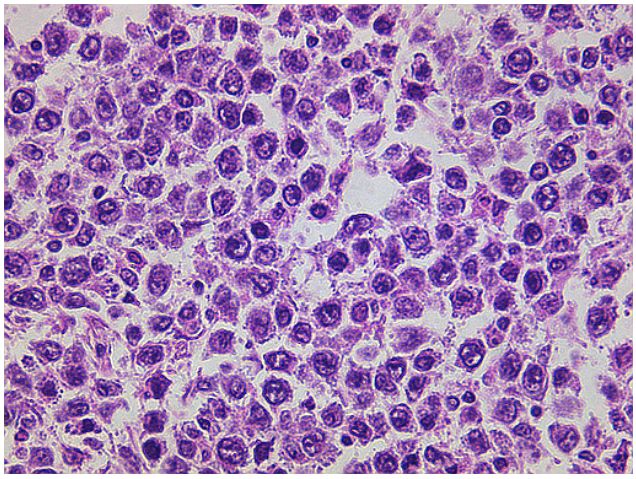

Fig. 7 Histopathological findings: Diffuse proliferation of atypical cells with irregular medium to large round or oval nuclei and a high N/C ratio.

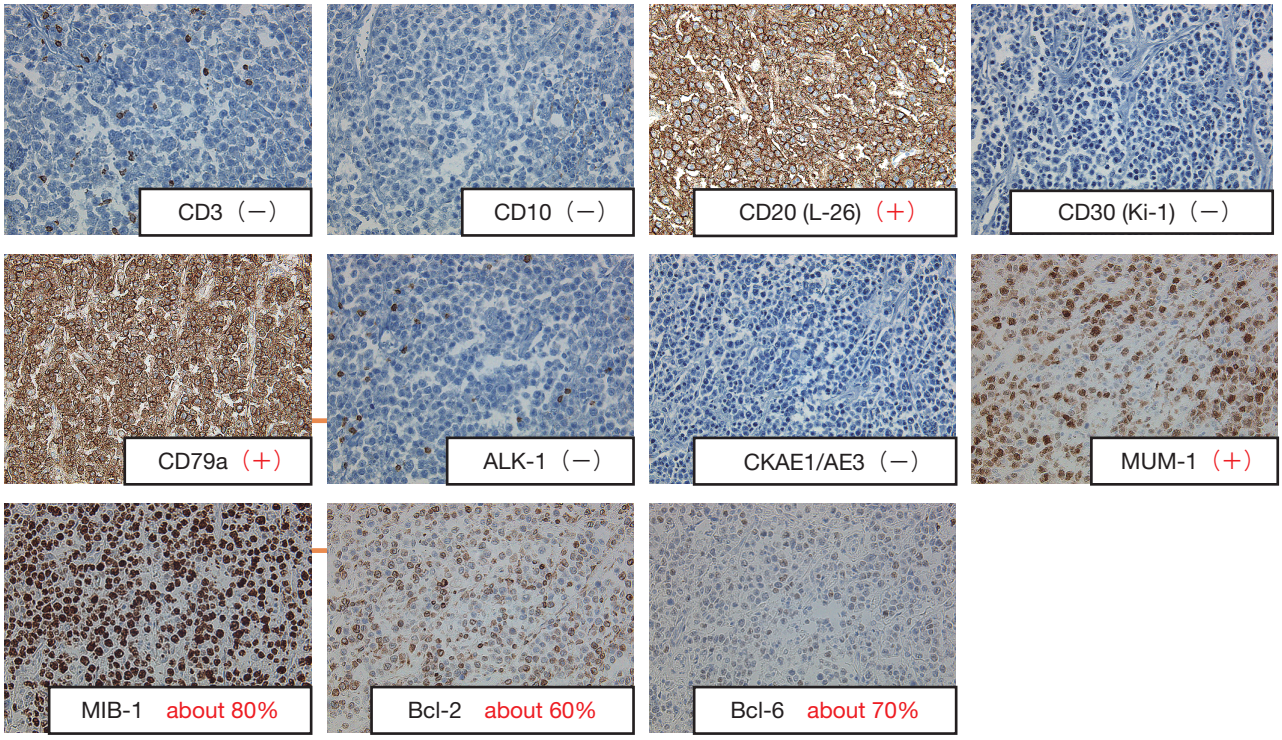

Fig. 8 Immunohistological examination: Findings were consistent with a diagnosis of diffuse large B cell lymphoma.

long-term management of chronic hepatitis C and also discussed the relevant literature.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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