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CASE REPORT

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Primary hepatic marginal zone B-cell lymphoma with mantle cell lymphoma phenotype

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Abstract We report a rare case of primary hepatic lymphoma, Stage II disease, in a 48-year-old male who had a solitary hepatic tumour measuring 4×4.5×3 cm. The tumour showed a nodular growth pattern and lymphoepithelial lesions with bile ducts. Some neoplastic nodules had a non-neoplastic atrophic germinal centre and/or a thin mantle cell layer. Morphologically, the neoplastic cells were centrocyte-like cells or intermediate lymphocytes. They expressed L26(CD20)$^+$/LN-1(CDw75)$^\pm$/LN-2(CD74)$^+$/cyclin D1$^-$ and had a monotypic immunoglobulin of cytoplasmic IgM (κ) on paraffin sections. The neoplastic cells or neoplastic nodules expressed surface IgM$^+$/surface IgD$^\pm$/Leu-1(CD5)$^+$/DRC-1$^+$/alkaline phosphatase$^+$/B1(CD20)$^+$/B4(CD19)$^-$ on fresh frozen sections. We therefore diagnosed this case as primary hepatic marginal zone B-cell lymphoma with mantle cell lymphoma phenotype. We confirm that it is difficult to differentiate extranodal marginal zone B-cell lymphoma (low grade B-cell lymphoma of mucosa-associated lymphoid tissue type; MALT lymphoma) and mantle cell lymphoma.

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Introduction

Primary hepatic lymphoma is a rare disease [24]; it accounts for 0.4% of all extranodal lymphomas [9]. Most cases of hepatic lymphoma are reported to be diffuse large cell B-cell lymphoma, a high grade lymphoma [7, 18, 20, 24].

Morphologically, the neoplastic cells of mantle cell lymphoma (MCL) are centrocyte-like cells or intermediate lymphocytes [22]. Phenotypically, the cells exhibit both surface (s) IgD and CD5 positivity [2, 10]. MCL is characterized by the t (11;14) translocation and its molecular counterpart bcl-1 rearrangement, which may result in an overexpression of the PRAD-1/cyclin D1 gene [3, 4, 21] and cyclin D1 protein expression [17, 23]. Extranodal MCL has been reported [8, 14, 15, 16, 19]. However, to our knowledge hepatic MCL has not been reported previously.

Extranodal marginal zone B-cell lymphoma (low grade B-cell lymphoma of MALT [mucosa-associated lymphoid tissue] type; MALT lymphoma) is characterized by the proliferation of centrocyte-like cells, monocytoid B-cells and small lymphocytes, and by lymphoepithelial lesions and follicular colonization. There is associated plasma cell differentiation. The tumour is slow growing and may arise from several extranodal organs [10, 11], including the liver [12]. This lymphoma shows a negative reaction for sIgD and CD5, and no rearrangement of the bcl-1 or the bcl-2 gene [10].

We report a rare case diagnosed as primary hepatic marginal zone B-cell lymphoma with MCL phenotype and discuss the difficulty of the differential diagnosis of extranodal marginal zone B-cell lymphoma and MCL.

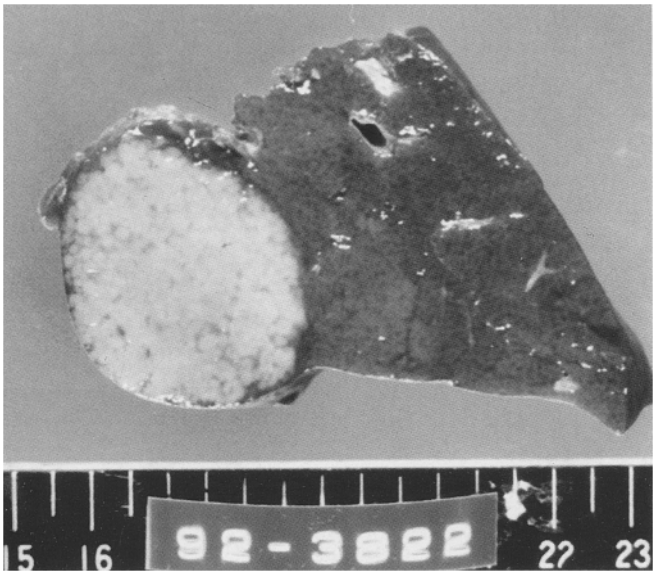

Fig. 1 The cut surface of the hepatic tumour, showing tiny nodules

Case report

The patient was a 48-year-old male in whom a nodular lesion in the left lobe of the liver was detected incidentally by abdominal ultrasonography. Positivity for hepatitis B surface (HBs) antigen was also determined at a routine health examination carried out on February 13, 1992. On May 6, he was admitted to the Juntendo University Hospital. Total serum protein was 7.7 g/dl, with globulin 3.0 g/dl. Peripheral blood leucocyte count was 8,100/mm^3, without atypical lymphocytes. Serum liver function test results were normal and levels of tumour markers were in the normal range; carcinoembryonic antigen 2.6 ng/ml, alpha-fetoprotein 5 ng/ml. Both HBs and HBe antigens were positive. A solitary intrahepatic nodule was detected as a hypoechoic area on ultrasound echography and as hypo- to avascular on computed tomography. There was no splenomegaly or superficial lymph node enlargement. On May 8, ultrasound-guided percutaneous needle biopsy of the hepatic tumour was performed (biopsy specimen). On May 25, 1992, he underwent partial hepatectomy (10×9×5 cm) of the lateral segment of the left lobe of the liver. A 4×4.5×3 cm well-circumscribed nodule (Fig. 1) was removed, and lymph nodes were resected from the porta hepatis, right stomach, lesser curvature and lesser omentum (surgical specimens). He received combination chemotherapy with cyclophosphamide (Endoxan), doxorubicin hydrochloride (Adriacin), vincristine sulphate (Oncovin) and prednisone. As of July 1995, he remains free of lymphoma.

Materials and methods

The biopsy specimen and the surgical specimens were fixed with 10% formaldehyde solution and embedded in paraffin for haematoxylin and eosin staining, histochemistry and immunostaining. The monoclonal and polyclonal antibodies used were: IgM, IgG, IgA, κ, λ, leucocyte common antigen (LCA, CD45), L26 (CD20), epithelial membrane antigen (EMA), neuron-specific enolase (NSE), S-100 protein, vimentin, desmin, lysozyme (DAKO, Copenhagen, Denmark), LN1 (CDw75), LN2 (CD74) (Techniclone International, Santa Ana, Calif., USA), MT1 (CD43, Bioscience, Emmerbruecke, Switzerland), UCHL-1 (CD45RO, Nichirei, Tokyo, Japan), cyclin D1 (clone 5D4, Aichi Cancer Center, Aichi, Japan) [3]. Before cyclin D1 immunostaining, the sections were irradiated with microwave. The sections were then incubated with monoclonal antibodies for 2 h at room temperature, followed by the avidin-biotin-peroxidase complex (Vector Laboratories, Burlingame, Calif., USA).

Part of the fresh surgical specimen excised from the hepatic tumour was embedded in OCT compound (Miles Laboratories, Elkhart, Ind., USA) and quick frozen in a mixture of dry ice and acetone. Sections (6 μm thick) were cut with a cryostat and fixed with cold acetone for 10 min. The monoclonal antibodies used were: dendritic reticulum cell-1 (DRC-1; DAKO), IgM, IgD, B1 (CD20), B4 (CD19), CALLA (CD10; Coulter Immunology, Hialeah, Fla., USA) and Leu-1 (CD5, Becton Dickinson, Mountain View, Calif., USA). Alkaline phosphatase (ALP) was stained with an ALP staining kit (Muto Chemicals, Tokyo, Japan).

Results

Biopsy specimen

The fragmented hepatic tumour biopsy specimen showed prolifertion of small lymphoid cells, intermediate lymphocytes and centrocyte-like cells. The atypical lymphocytes were strongly positive for LCA, positive for L26 and negative for MT1, UCHL-1, S-100 protein, vimentin, desmin, NSE, EMA, lysozyme, Grimelius, and Fontana Masson. A diagnosis of MCL was made on the basis of the findings by haematoxylin and eosin staining.

Surgical specimens

The hepatic tumour exhibited a nodular growth pattern consisting of centrocyte-like cells or intermediate lymphocytes (Fig. 2a). Small lymphoid cells and small cleaved cells were admixed with neoplastic nodules. A small number of blastoid cells was observed. Small foci of atrophic germinal centres and/or a thin mantle cell layer were observed in some neoplastic nodules (Fig. 2a). Lymphoepithelial lesions comprising bile ducts with neoplastic cells were seen (Fig. 2b). Neither plasma cells nor monocytoid B cells were observed. Monoclonal cytoplasmic immunoglobulin staining, IgM κ type, was shown in the neoplastic nodules. On the paraffin sections, the neoplastic cells were strongly positive for L26 and LN2, weakly positive for LN1 and negative for cyclin D1. On the frozen sections, the neoplastic cells were positive for sIgM and B1, Leu-1 (Fig. 3a) and ALP, weakly positive for CALLA and sIgD (Fig. 3b) and negative for B4. The neoplastic nodules exhibited a meshwork pattern with DRC-1 antibody. We diagnosed this case as primary hepatic marginal zone B-cell lymphoma with MCL phenotype. Numerous neoplastic nodules similar to those in the hepatic tumour were seen in the lymph nodes of the lesser omentum, lesser curvature and porta hepatis, but not in the right gastric lymph nodes. The remaining liver parenchyma showed chronic inactive hepatitis.

Discussion

We diagnosed primary hepatic lymphoma in our patient according to the criteria established by Caccamo et al.

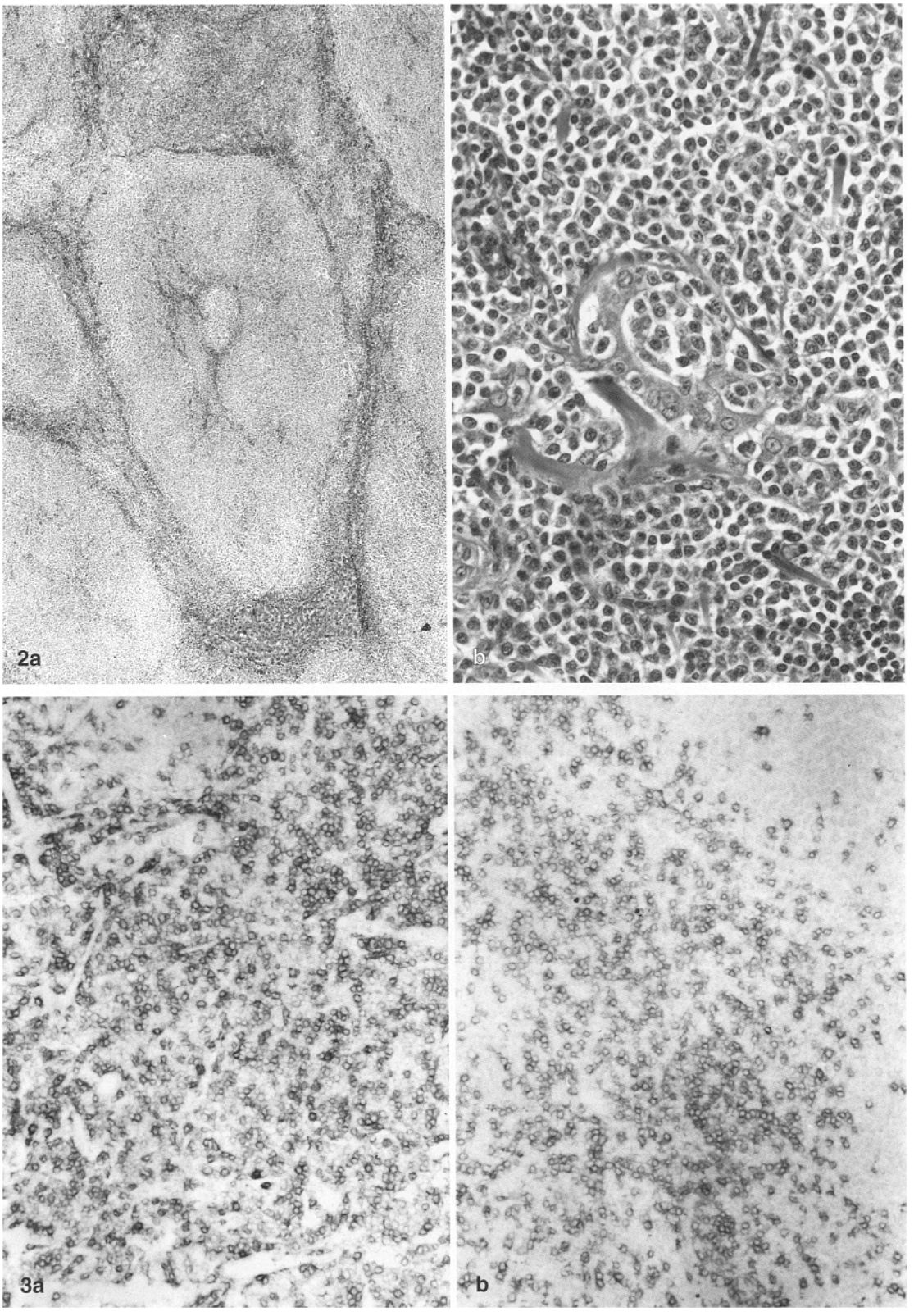

Fig. 2 Hepatic tumour showing a nodular growth pattern around atrophic germinal centres and a thin mantle cell layer (**a** ×65) and lymphoepithelial lesions with bile ducts with neoplastic centrocyte-like cells (**b** ×325). Haematoxylin and eosin staining

Fig. 3 The neoplastic cells are positive for Leu-1 (**a** ×160) and weakly positive for surface IgD (**b** ×160)

[5], who noted that the diagnosis can be established clinically in a patient who presents with primary symptoms of liver disease, abnormal results of a liver biopsy, no palpable superficial lymphadenopathy or splenomegaly, normal thoracic computed tomographic scans and nor-

mal bone marrow and blood counts for at least 6 months after the time of the liver biopsy.

We diagnosed primary hepatic marginal zone B-cell lymphoma from the following findings; a nodular growth pattern consisting of centrocyte-like cells or intermediate lymphocytes with monoclonal cytoplasmic immunoglobulin staining, IgM κ light chain and lymphoepithelial lesions with bile ducts and cyclin D1$^-$. The CD5$^+$/DRC-1$^+$/sIgD$^\pm$/LN2$^+$ findings in our patient imply that this is MCL [6, 8, 13, 14, 15]. The ALP$^+$/cyclin D1$^-$ findings and the lymphoepithelial lesions with bile ducts in the patient imply that this is a marginal zone B-cell lymphoma [10, 11]. Definite nuclear staining was seen in 15 of 15 MCL and in 0 of 4 MALT lymphomas in which immunoperoxidase staining with polyclonal cyclin D1 antibody was used [23]. Similarly, a positive nuclear pattern was seen in 17 (85%) of 20 cases of MCL in specimens reacted with the same monoclonal cyclin D1 antibody, clone 5D4, used in our study [17]. From the immunophenotypic findings of sIgD$^\pm$/Leu-1$^+$/DRC-1$^+$/ALP$^+$/LN-2$^+$/cyclin D1$^-$, therefore, we believe that this case is a marginal zone B-cell lymphoma with MCL phenotype. Small lymphocytes in the inner layer of the mantle zone of the lymph node have been sham to be CD5$^+$/sIgD$^+$/ALP$^-$, and small lymphocytes in the outer layer of the mantle zone and in the marginal zone of the spleen exhibit CD5$^-$/sIgD$^-$/ALP$^+$ [1]. These reports and our case indicate that it may be difficult to distinguish marginal zone B-cell lymphoma from MCL.

Fraga et al. [8] reported four patients with mucosal; gastric, large intestinal and tonsillar MCL who had a monomorphic picture of centrocytes arranged in a diffuse or vague nodular pattern, as well as lymphoepithelial lesions; they showed a CD5/sIgD phenotype, loose aggregates of DRC and PRAD-1/cyclin D1 overexpression on northern blot analysis. Isaacson et al. [12] reported four cases of primary hepatic low-grade B-cell lymphoma of MALT type (MALT lymphoma or extranodal marginal zone B-cell lymphoma); these patients' specimens showed centrocyte-like cells surrounding reactive follicles and forming lymphoepithelial lesions with bile ducts. Isaacson et al. [12] did not describe sIgD, CD5, ALP, DRC-1 and cyclin D1 immunostaining reactivity. It is interesting to consider whether marginal zone B-cell lymphoma is related to MCL. The cases reported by Fraga et al. [8] and Isaacson et al. [12] suggest the difficulty in making a differential diagnosis of extranodal MCL and marginal zone B-cell lymphoma, as well as suggesting the existence of patients with CD5 positive and/or sIgD positive marginal zone B-cell lymphoma.

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References

1. Abe M, Tominaga K, Wakasa H (1994) Phenotypic characterization of human B-lymphocyte subpopulations, particularly human CD5$^+$ B-lymphocyte subpopulation within the mantle zones of secondary follicles. Leukemia 8:1039–1044
2. Banks P, Chan J, Cleary M, et al (1992) Mantle cell lymphoma: a proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol 16:637–640
3. Banno S, Yoshikawa K, Nakamura S, et al (1994) Monoclonal antibody against PRAD1/cyclin D1 stains nuclei of tumor cells with translocation or amplification at BCL-1 locus. Jpn J Cancer Res 85:918–926
4. Bosch F, Jares P, Campo E, et al (1994) PRAD-1/cyclin D1 gene overexpression in chronic lymphoproliferative disorders. a highly specific marker of mantle cell lymphoma. Blood 84:2726–2732
5. Caccamo D, Pervez NK, Marchevsky A (1986) Primary lymphoma of the liver in the acquired immunodeficiency syndrome. Arch Pathol Lab Med 110:553–555
6. Chilosi M, Pizzolo G, Fiore-Donati L, Bofill M, Janossy G (1983) Routine immunofluorescent and histochemical analysis of bone marrow involvement of lymphoma/leukemia: the use of cryostat sections. Br J Cancer 48:763–775
7. Dement SH, Mann RB, Staal SP, Kuhajda FP, Boitnott JK (1987) Primary lymphomas of the liver. Report of six cases and review of the literature. Am J Clin Pathol 88:255–263
8. Fraga M, Lloret E, Sarchez-Verde L, et al (1995) Mucosal mantle cell (centrocytic) lymphomas. Histopathology 26:413–422
9. Freeman C, Berg JW, Cutler SJ (1972) Occurrence and prognosis of extranodal lymphomas. Cancer 29:252–260
10. Harris NL, Jaffe ES, Stein H, et al (1994) A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood 84:1361–1392
11. Isaacson PG, Spencer J (1987) Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 11:445–462
12. Isaacson PG, Banks PM, Best PV, McLure SP, Konrad Muller-Helmelink H, Wyatt JI (1995) Primary low-grade hepatic B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type. Am J Surg Pathol 19:571–575
13. Juneja SK, Pilkington GR, Ironside PNJ, Wolf MM, Ding JC, Cooper IA (1986) The phenotype of mantle zone lymphoma studied by monoclonal antibodies. Pathology 18:131–136
14. Mori N, Oka K, Kojima M (1988) DRC antigen expression in B-cell lymphomas. Am J Clin Pathol 89:488–492
15. Mori N, Oka K, Kojima M (1988) Immunohistochemical study of mantle zone lymphoma. Am J Clin Pathol 90:143–148
16. Mori N, Oka K, Ishido T, Nakamura K (1991) Primary gastric mantle zone lymphoma. Arch Pathol Lab Med 115:603–606
17. Nakamura S, Seto M, Banno S, et al (1994) Immunohistochemical analysis of cyclin D1 protein in hematopoietic neoplasms with special reference to mantle cell lymphoma. Jpn J Cancer Res 85:1270–1279
18. Ohsawa M, Aozasa K, Horiuchi K, et al (1992) Malignant lymphoma of the liver. Report of five cases and review of the literature. Dig Dis Sci 37:1105–1109
19. Oka K, Mori N, Yatabe Y (1993) Immunohistochemical characteristics of monocytoid B cell lmyphoma, mantle zone lymphoma, small lymphocytic lymphoma (or B chronic lymphocytic leukemia), and hairy cell leukemia. Acta Haematol (Basel) 90:84–89
20. Osborne BM, Butler JJ, Guarda LA (1985) Primary lymphoma of the liver. Ten cases and a review of the literature. Cancer 56:2902–2910
21. Raffeld M, Jaffe ES (1991) bcl-1, t (11,14) and mantle cell derived lymphomas. Blood 78:259–263
22. Weisenburger DD (1984) Mantle zone lymphoma: an immunohistologic study. Cancer 53:1073–1080
23. Yang W-L, Zuckerberg LR, Motokura T, Arnold A, Harris NL (1994) Cyclin D1 (Bcl-1, PRAD1) protein expression in low-grade B-cell lymphomas and reactive hyperplasia. Am J Pathol 145:86–96
24. Zafrani ES, Gaulard P (1993) Primary lymphoma of the liver. Liver 13:57–61