

Original Article

Characteristics of CD5-Positive Splenic Marginal Zone Lymphoma with Leukemic Manifestation ; Clinical, Flow Cytometry, and Histopathological Findings of 11 Cases

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Splenic marginal zone lymphoma (SP-MZL) is a rare low-grade B-cell neoplasm that often shows leukemic manifestation. Less than 20% of cases of SP-MZL express CD5. We analyzed 11 cases of CD5-positive SP-MZL with leukemic manifestation. The clinical characteristics of these cases did not differ from those of CD5-negative SP-MZL. Flow cytometry revealed positive results as follows : CD3, 0/9 ; CD5, 11/11 ; CD10, 0/11 ; CD11c, 4/10, CD13, 5/11 ; CD19, 11/11 ; CD20, 10/11 ; CD21, 4/4 ; CD22, 7/7 ; CD23, 5/10 ; CD25, 8/11 ; FMC7, 5/7 ; κ type 6/9, and λ type 2/9. All 3 cases with monoclonal γ -globulinemia expressed CD13. Resected spleen exhibited a proliferation of neoplastic cells in white pulp in all 8 splenectomy patients and a marginal pattern was detected in 5 patients. Only 2 cases showed involvement of red pulp. Immunohistochemistry showed that the lymphoma cells were positive for CD5, CD20, and BCL-2 and negative for CD3, CD10, cyclin D1, BCL-6, and MUM-1 in all 11 cases. These results suggest that CD5-positive SP-MZL differs from B-cell chronic lymphocytic leukemia, that CD13 expression is found in about half of CD5-positive SP-MZL cases, and that CD5-positive SP-MZL may be related to memory B-cell neoplasm or plasma cell differentiation. [*J Clin Exp Hematopathol* 50(2) : 107-112, 2010]

Keywords: splenic marginal zone lymphoma, CD5, CD13, immunohistochemistry

INTRODUCTION

CD5-positive B-cells are distinct from CD5-negative B-cells in anatomic localization, immunophenotype, gene usage, and function.¹⁻³ The CD5⁺ B-cell subpopulation comprises B-cells that vary in number throughout life and can produce a

disproportionate level of low-affinity and poly-specific auto-antibodies. CD5 is also expressed to varying degrees by mature B-cell neoplasms including most cases of B-cell chronic lymphocytic leukemia (B-CLL), small lymphocytic lymphoma, and mantle cell lymphoma, as well as 20% of cases of lymphoplasmacytic lymphoma, 10% to 20% of cases of hairy cell leukemia (HCL), 5% to 10% of cases of diffuse large B-cell lymphoma, and, rarely, in follicular lymphoma.⁴⁻⁵ Thus, CD5⁺ B-cells appear to be counterpart cells in all lymphoma/leukemia subtypes.

SP-MZL is a rare and indolent lymph-proliferative disease.⁶⁻⁸ SP-MZL presents with marked splenomegaly, and is often associated with leukemic manifestation.⁹ Cases with circulating atypical villous lymphocytes are known as splenic lymphoma with villous lymphocytes. In these cases, the spleen is histologically characterized by a marginal zone pattern with small- to medium-sized lymphoma cells, or by a nodular infiltrating pattern based on pre-existing white pulp. The bone marrow (BM) is involved in most cases. SP-MZL cells normally express CD20 and IgM, and sometimes IgD,

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but not CD3, CD10, CD23, CD43, Bcl-6, or cyclin D1. Less than 20% of SP-MZL cells express CD5 antigen.⁷⁻¹¹

Although CD5⁺ SP-MZL differs from B-CLL in morphology and immunophenotypic markers, the differential diagnosis between CD5⁺ SP-MZL and B-CLL is sometimes difficult. Moreover, in the World Health Organization classification 4th edition, splenic lymphoma/leukemia, unclassifiable, is described as a very rare indolent B-cell lymphoma, which generally presents as splenomegaly with involvement of the BM and PB. This term is used when the clinical findings of patients do not fall into any of the categories of B-cell lymphoid neoplasm recognized by the World Health Organization classification system.¹²

In this study, we analyzed 11 cases of CD5⁺ SP-MZL with leukemic manifestation by clinical, flow cytometric, histopathological, and immunohistochemical analyses.

MATERIALS AND METHODS

Case selection

Eleven cases (4 males, 7 females; 35 to 91 years; median 63 years) of CD5⁺ B-cell chronic lymphoproliferative disorders were analyzed. All patients showed circulating CD5⁺ B-cells in their peripheral blood (PB) and involvement of BM. Lymphocytes in the PB and BM were comprised of small mature lymphocytes and atypical lymphocytes. All patients exhibited villous lymphocytes or monocytoid cells. Villous lymphocytes were demonstrated by May-Giemsa staining of PB or by electron microscopy of PB mononuclear cells. Monocytoid cells were demonstrated by histopathologic examination of BM or spleen tissue.

Clinical data and immunohistochemistry

Patient age, sex, lactate dehydrogenase (LDH), interleukin-2 receptor, white blood cell count, and the numbers of lymphocytes in PB and BM were recorded. Flow cytometric analysis of mononuclear cells of PB and BM was performed using various monoclonal antibodies against CD3, CD5, CD10, CD11c, CD13, CD19, CD20, CD21, CD22, CD23, CD25, FMC7, and κ , with that of κ performed by a commercially based analysis. Markers that were expressed on more than 20% of cells were regarded as positive markers. A splenectomy was performed in 8 patients (patients 1-3, and 6-10). A BM biopsy and/or clot sections were obtained from 6 patients (patients 2, 4, 5, 8, 9, and 11). Resected tissue was fixed in 20% formalin for routine histopathology and immunohistochemistry using Bond-Max (Leica Japan, Tokyo, Japan). Antibodies against CD3, CD5, CD10, CD20, BCL-2, BCL-6, κ , λ (Novocastra, Newcastle upon Tyne, UK), cyclin D1 (Nichirei, Tokyo, Japan), and MUM-1 (Abcam, Cambridge, USA) were also used in this study.

RESULTS

The clinical data of the patients is listed in Table 1. The white blood cell counts varied from 4,000/cmm to 24,800/cmm and the proportion of lymphocytes including atypical lymphocytes ranged from 22% to 97%, indicating an absolute lymphocyte count of between 2,240 and 15,405. LDH was within the normal limits. Interleukin-2 receptor was elevated, and ranged between 1,060 and 10,100. Physical examination and neck-abdominal CT showed that all patients had splenomegaly. Lymph node swelling at initial presentation was only found in 1 patient (patient 2). Patient 6 showed no lymph node swelling at the initial diagnosis, but later swelling

Table 1. Clinical data of 11 cases of CD 5⁺ splenic marginal zone B-cell lymphoma

Case number	Age/sex	WBC (/cmm)	Lymphocytes		Splenomegaly	LN swelling	LDH (IU/mL)	IL-2 R (IU/mL)	Monoclonal gammopathy	HBV, HCV
			in PB (%)	in BM (%)						
1	63/M	10,000	51%	71%	Yes	No	172 (WNL)	1,060 (UNL)	IgM- κ	Negative
2	68/M	24,800	61%	76%	Yes	Yes	135 (WNL)	1,380 (UNL)	No	Negative
3	35/F	19,500	79%	52%	Yes	No	189 (WNL)	3,540 (UNL)	IgM	Negative
4	91/F	4,500	73%	66%	Yes	No	203 (WNL)	1,400 (UNL)	No	Negative
5	63/M	20,400	70%	54%	Yes	No	120 (WNL)	-	No	Negative
6	78/M	19,600	22%	ne	Yes	No→Yes	255 (WNL)	10,100 (UNL)	No	Negative
7	55/F	4,000	56%	35%	Yes	No	214 (WNL)	1,360 (UNL)	No	Negative
8	58/F	6,800	41%	32%	Yes	No	175 (WNL)	1,280 (UNL)	IgM- κ	Negative
9	65/F	7,400	97%	96%	Yes	No	345 (WNL)	5,150 (UNL)	No	Negative
10	48/F	6,300	61%	ne	Yes	No	191 (WNL)	2,290 (UNL)	No	Negative
11	65/F	16,700	85%	44%	Yes	No	160 (WNL)	1,540 (UNL)	No	Negative

WBC, white blood cell; PB, peripheral blood; BM, bone marrow; LN, lymph node; LDH, lactate dehydrogenase; IL-2 R, interleukin-2 receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; WNL, within normal limit; UNL, upper normal limit; ne, not examined.

was noted. Monoclonal γ -globulinemia was detected in 3 patients. No abnormal elevation of anti-titer for hepatitis B or C virus was found in any patients. Information about the weight of the resected spleen without previous chemotherapy was available in 3 cases and ranged from 1,200 to 1,650 g with an average of 1,416 g. All 11 patients presented with an indolent clinical course and have survived.

Small mature lymphocytes with a round nucleus, and small- to medium-sized lymphocytes with a round or slightly irregular-shaped nucleus and mild to intermediate cytoplasm, were observed in PB and BM. Lymphocytes twice as large as erythrocytes with prominent nucleoli and slightly basophilic cytoplasm were intermingled among the other cells (Fig. 1a). Villous lymphocytes were detected in patients 1 and 4 by electron microscopy (Fig. 1b) and in patients 8 to 12 by PB smear without blowing.

The immunologic markers of the neoplastic cells in PB or BM are listed in Table 2. The flow cytometry results were as follows (positive cases/examined cases, more than 20% as positive): CD3, 0/9; CD5, 11/11; CD10, 0/11; CD11c, 4/10, CD13, 5/11; CD19, 11/11; CD20, 10/11; CD21, 4/4; CD22, 7/7; CD23, 5/10; CD25, 8/11; and FMC7, 5/7. The light chain of surface immunoglobulin was as follows: κ type 6/9 and λ type 2/9. The histology and immunohistochemistry findings for the spleen tissue and BM are listed in Table 3. Resected spleen exhibited proliferation of neoplastic cells in white pulp in all 8 splenectomy patients. Among them, proliferation of neoplastic cells in the marginal zone of the white pulp was detected in 5 patients (Fig. 1c). For these 5 patients, splenectomy was performed before chemotherapy. Nodular proliferation in the white pulp was seen in the other 3 patients. Splenectomy in these 3 patients was performed after combination chemotherapy. Infiltration of neoplastic cells into the red pulp was only found in 2 patients. The lymphoma cells exhibited small- to medium-sized and slightly irregular-shaped nuclei with clear cytoplasm (Fig. 1d). Immunohistochemistry showed that the lymphoma cells were positive for CD5, CD20, and BCL-2, and negative for CD3, CD10, cyclin D1, BCL-6, and MUM-1 in all 11 cases. BM clot and biopsy section revealed a nodular or interstitial diffuse proliferation pattern of the lymphoma cells (Fig. 1e).

DISCUSSION

We analyzed 11 cases with CD5⁺ splenic lymphoma with leukemic manifestation. These patients had leukemic proliferation of CD5⁺ B-cells with atypical morphology and splenomegaly. Although differential diagnosis of B-CLL from CD5⁺ SP-MZL is sometimes challenging, we found morphological heterogeneity of circulating lymphocytes in the latter cases. Circulating lymphocytes consisted of small- to medium-sized lymphocytes with a round or indented nucleus and condensed chromatin and occasional lymphocytes with

nuclear clefts. Small- to medium-sized lymphoid cells with relatively abundant pale cytoplasm that resembled monocytoid cells and lymphoplasmacytic cells were also seen. In some cases, villous lymphocytes were demonstrated by May-Giemsa staining and electron microscopy. These morphological findings indicated SP-MZL, but not B-CLL.

The clinical characteristics of our 11 patients did not appear to differ from those of CD5⁺ SP-MZL.⁴⁻⁶ SP-MZL typically affects elderly or middle-aged patients in the sixth decade without gender predominance. Splenomegaly, lymphocytosis, and cytopenia are important characteristics. Lymphadenopathy and/or other organ involvement are infrequent, but may develop during the course of the disease. B symptoms and an increase in LDH are rare at presentation. The clinical course is usually chronic and indolent. Less than one-third of patients have monoclonal proteinemia. The clinical features of our series were almost identical to those reported for SP-MZL. Although hepatitis B or C virus has been suggested to have a pathogenic role in SP-MZL in Western countries, no patients with abnormal elevation of hepatitis B and C virus anti-titer were detected in our series. No autoimmune phenomena were present either.

Splenectomy remains one of the primary treatment options for patients fit for surgery. In our series, 5 patients received splenectomy first. In the subsequent histological evaluation, monocytoid cells with a round or slightly indented nucleus and abundant clear cytoplasm were found to be common. The marginal zone proliferation pattern was found in the 5 patients who underwent splenectomy before any treatment confirmed that these cases were SP-MZL. The 3 patients who underwent splenectomy after combined chemotherapy did not show the marginal zone proliferation pattern, but the marginal proliferation pattern may have disappeared in these patients owing to a decrease in the number of neoplastic cells. We considered a more accurate diagnosis for the other 3 patients who did not undergo splenectomy to distinguish SP-MZL from the other cases of low-grade B-cell lymphoma/leukemia such as HCL. All 3 patients were negative for CD11c. Robbins *et al.* reported that CD11c results were positive in all 161 cases of HCL.¹³ This indicates that negativity for CD11c could exclude the possibility of HCL. Histological analysis revealed that the neoplastic cells of all 11 patients showed monocytoid features. On the basis of the findings in our 11 patients, CD5⁺ SP-MZL may not be as rare as previously thought.¹⁴ No diffuse infiltration of the neoplastic cells in the red pulp was found in our series, which excluded the possibility of HCL. In our series, the lymphoma cells infiltrated BM with a nodular or interstitial diffuse proliferation pattern. Although the intra-sinusoidal proliferation pattern is typical for BM involvement of SP-MZL, Inamdar *et al.* reported that the most frequent patterns were nodular (87%) and interstitial (63%).¹⁵

Flow cytometric analysis of leukemic cells from PB and/

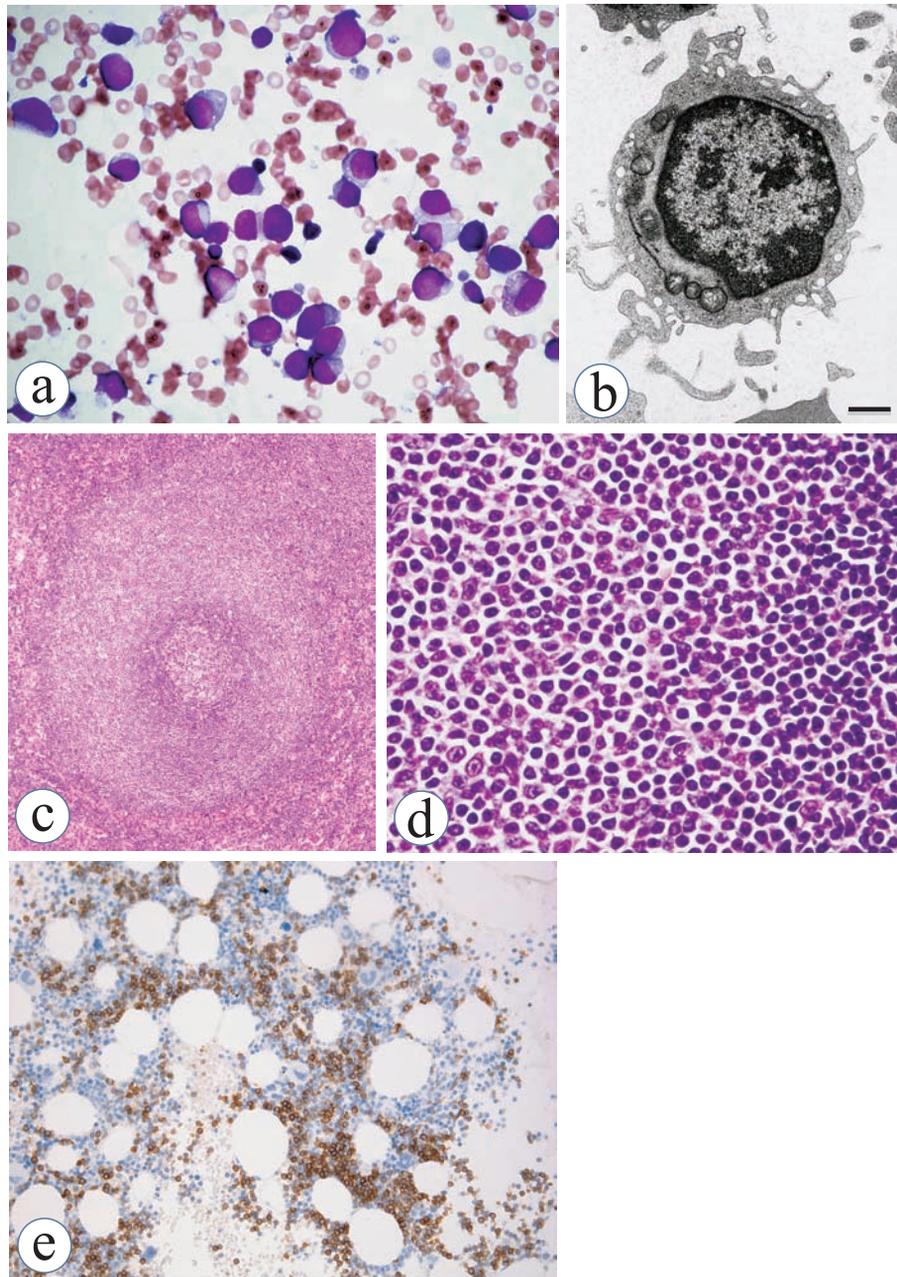


Fig. 1. Histological and immunohistopathological findings of CD5⁺ splenic marginal zone lymphoma. *(1a)* Peripheral blood smear, May-Giemsa staining for patient 3. Leukemic lymphocytes consist of small mature lymphocytes with a round or indented nucleus and small- to medium-sized lymphocytes with larger-sized nuclei and clear cytoplasm. Original magnification $\times 400$. *(1b)* Bone marrow lymphocyte, electron microscopy for patient 1. A leukemic lymphocyte has short and unevenly distributed villi. Bar = 1 μm . Original magnification $\times 6,000$. *(1c)* Section of resected spleen. H&E staining for patient 2. In white pulp, a bright and thickened marginal zone surrounds the mantle zone and germinal center. Original magnification $\times 40$. *(1d)* Section of resected spleen. H&E staining for patient 2. In the marginal zone of *(1c)*, lymphocytes with small- to medium-sized nuclei and clear cytoplasm are present. Original magnification $\times 400$. *(1e)* Section of bone marrow clot. Immunohistochemistry with CD20 for patient 4. CD20-positive cells are clustered and scattered. Original magnification $\times 100$.

Table 2. Flow cytometric markers of 11 cases of CD5⁺ splenic marginal zone B-cell lymphoma

Case number	BM/PB	CD3	CD5	CD10	CD11c	CD13	CD19	CD20	CD21	CD22	CD23	CD25	FMC7	κ	λ
1	(BM)	-	94	3	43	89	96	97	96	94	10	89	40	90	0
2	(PB)	1	78	1	79	18	95	33	-	-	11	31	-	0	0
3	(PB)	14	63	0	-	68	81	83	26	-	1	11	-	-	-
4	(BM)	-	85	0	3	1	85	79	53	-	22	15	11	1	14
5	(BM)	13	91	0	8	83	96	99	86	87	53	43	65	23	0
6	(BM)	13	56	0	5	8	54	0	-	-	-	56	-	30	4
7	(BM)	16	66	12	14	17	70	77	-	92	56	53	-	22	56
8	(BM)	16	40	2	8	44	68	43	-	82	11	69	0	82	0
9	(PB)	8	56	0	38	6	91	89	-	88	13	86	21	-	-
10	(PB)	12	51	0	24	3	62	59	-	52	26	9	59	70	3
11	(BM)	14	47	0	19	58	79	65	-	98	70	89	42	76	0

BM, bone marrow ; PB, peripheral blood ; -, not tested. Flow cytometric analysis of mononuclear cells in peripheral blood or bone marrow cells shows percentage of positive cells. Positive percentage more than 20% is bold.

Table 3. Histopathologic pattern of 11 cases of CD5⁺ splenic marginal zone B-cell lymphoma

Case number	PB/BM		Spleen				
	Monocytoid cells	Villous cells	Splenectomy	Spleen weight	White pulp		Red pulp Involvement
					Involvement	Pattern	
1	Yes	Yes (EM)	Yes	1400 g	Yes	Marginal	No
2	Yes	No information	Yes	No information	Yes	Marginal	No
3	Yes	No information	Yes	1,650 g	Yes	Marginal	No
4	Yes	Yes (EM)	No	-	-	-	-
5	Yes	No information	No	-	-	-	-
6	Yes	No information	Yes*	No information	Yes	Nodular	No
7	Yes	Yes (PB)	Yes*	No information	Yes	Nodular	No
8	Yes	Yes (PB)	Yes	1,200 g	Yes	Marginal	No
9	Yes	Yes (PB)	Yes*	No information	Yes	Nodular	Yes
10	Yes	Yes (PB)	Yes	No information	Yes	Marginal	Yes
11	No	Yes (PB)**	No	-	-	-	-

Yes, Splenectomy was performed before chemotherapy. Yes*, Splenectomy was performed after chemotherapy. EM, Villous cells were detected by electron microscopy. PB, Villous cells were detected by peripheral blood smear without blowing. -, not tested; **, κ⁺ plasma cells.

or BM revealed that 5 of 11 SP-MZL cases expressed CD13. CD13 is one of the myelomonocytic markers and its expression by a lymphoid neoplasm has only previously been reported for precursor B- and T-cell neoplasms, anaplastic large cell lymphoma, and B-CLL.¹⁶⁻¹⁹ The frequency of CD13 expression in low-grade B-cell lymphoma is reported to range from 1.9% to 50%,¹⁹⁻²³ and Kampalath *et al.* recently reported that 17.1% of 117 B-CLL cases showed expression of CD13.²⁴ The biological significance of CD13 expression is not well understood, but it is reported that patients with aberrant markers, including CD13, have markedly decreased overall survival compared with patients without aberrant markers. Further studies are required to confirm the prognostic significance of CD13 expression in SP-MZL ; CD13 expression

was seen in half of the CD5⁺ SP-MZL cases in this study. We demonstrated that CD13 expression was found in not only B-CLL but also CD5⁺ SP-MZL. Moreover, all 3 cases with monoclonal γ-globulinemia in our series expressed CD13. These may indicate that CD13 expression is related to memory B-cells and plasma cell differentiation. CD23 was detected in 3 of 11 patients in the present study. Although co-expression of CD23 and CD5 in leukemic B-cells is characteristic of B-CLL, CD23 is also expressed in 30% of CD5⁺ SP-MZL cases.²⁵ CD23 is not unique for B-CLL, but is also expressed in some neoplastic memory B-cells.

In conclusion, CD5⁺ SP-MZL differs from B-CLL. The resected spleen exhibited proliferation of neoplastic cells in white pulp with or without a marginal zone proliferation pattern and

only two cases showed involvement of red pulp. CD13 is expressed in about half of CD5⁺ SP-MZL cases and may be related to memory B-cell neoplasm or plasma cell differentiation.

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