

Invited Paper

A study of so-called marginal zone lymphoma of the lymph node as a distinct disease entity

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Summary

We have already studied 21 cases of mantle cell lymphoma in the lymph node. Of these, we found 3 cases with the distinctive histologic and phenotypic findings of the lymphoma cells and reactive cells. Each of the 3 cases presented zonal proliferation of medium-sized lymphoma cells with round nuclei in the mantle zone and paracortex. The lymphoma cells were alkaline phosphatase (ALPase)⁺, CD5 (Leu1)⁻, CD10 (CALLA)⁻, CD25 (IL-2 α receptor)⁻, and showed a high anti-proliferating cell nuclear antigen/cyclin (PCNA/c) rate. Prominent reaction of interdigitating dendritic cells and histiocytes was found. The phenotypic findings of the lymphoma cells in the 3 cases are consistent with those of so-called marginal zone lymphocytes, and the cells had the different cytologic and histologic findings from mantle cell lymphoma and monocytoid B-cell lymphoma. Each of the 3 patients suffered from superficial lymphadenopathy, but there was no involvement of the lymphoma in the gastrointestinal tract and salivary gland. From the results, we suggest that the lymphoid neoplasm arises in marginal zone lymphocytes, and rarely occurs in the lymph node.

Key words: mantle cell lymphoma, marginal zone lymphoma, monocytoid B-cell lymphoma

Introduction

Banks et al¹⁾ proposed the term mantle cell lymphoma for the almost same entity centrocytic lymphoma, intermediate lymphocytic lymphoma and mantle zone lymphoma, because these 3 types of lymphoma may be the neoplastic counterpart of CD5 (Leu1)⁺ and CD10 (CALLA)⁻ lymphocytes, normally present in the follicular mantle²⁻⁵⁾. However, lymphocytes in the mantle zone and mantle cell lymphoma show no constant expression of CD5 in the lymph node^{2,4,6,7)}. In addition, Van den Oord⁸⁾, and Van Krieken^{9,10)} found a subpopulation of ALPase⁺, SIgM⁺, SIgD⁻, CD5⁻, CD25 (IL-2 α receptor)⁻, CD10⁻, and CD11c (LeuM5)⁻ B lymphocytes in the reactive lymph nodes. These lymphocytes are usually found in the splenic marginal zone, but rarely seen in lymph nodes. Furthermore, Van den Oord et al¹¹⁾ strongly suggested that the mantle zone lymphoma of the 7 examined cases was derived from SIgM⁺, ALPase⁺, CD5⁻, and CD10⁻ marginal zone lymphocytes, which had different phenotype and histologic features from mantle cell lymphoma.

We compared the cytohistologic, enzyme, and immuno-histochemical characteristics of mantle cell lymphoma, B-chronic lymphocytic leukaemia (B-CLL), lymphoplasmacytic/cytoid (Immunocytoma), monocytoid B cell (MBCL), and centroblastic/centrocytic lymphoma. In the cases of mantle cell lymphoma, we found 3 cases of lymphoma possessing the characteristics of marginal zone lymphocytes. In the updated Kiel classification, marginal zone lymphoma is included in the category of MBCL¹²⁾. We demonstrated the distinct clinicopathologic characteristics of

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so-called marginal zone lymphoma in the lymph node to be different from those of MBCL.

Patients and Methods

Histology, Enzyme, and Histochemistry

Twenty one cases of mantle cell lymphoma (including so-called marginal zone lymphoma) were selected from 230 cases of B cell lymphoma in the lymph node registry of the Department of Pathology, Fukuoka University. Twenty five cases of B-CLL, immunocytoma, centroblastic/centrocytic lymphoma and MBCL were also examined. The lymph nodes biopsied from the untreated patients were prepared for routine histologic examination. Hematoxylin-eosin, periodic acid Schiff, silver impregnation, and Giemsa stains were performed on B-5 and/or 10% formalin-fixed paraffin-embedded materials.

Nuclear features of the lymphoma cells were classified into three types: round, cleaved with small indented and hyperchromatic nuclei, and cleaved with a few deep lobulations. Paraffin-embedded and liquid nitrogen frozen tissue sections were studied immunohistochemically, using the alkaline phosphatase-conjugated avidin-biotin complex method. Table 1 lists the antibodies and single enzyme used. Anti-proliferating cell nuclear antigen (PCNA/c)⁺ cells were counted in 3 high power fields (HPFs) of the lymphoma cell infiltration by ocular manometer (Olympus OCM 10/10x10)¹³⁾. A minimum of 500 mononuclear cells were counted in each field. S100⁺ interdigitating dendritic cells (IDCs) and lysozyme⁺ histiocytes were counted in 8 HPFs of invasive foci by the same

manometer, and corrected to 1 mm³. The proliferating rate, the numbers of IDCs and histiocytes were analyzed by Student's t test. Cell surface study of blood mononuclear cells was done in patients with atypical lymphocytosis by FACScan (Becton Dickinson). For ALPase demonstration, the method using naphthol AS-BI phosphate and neu fuchsin in pH 9.3, 0.2 M tris-HCL buffer was used¹⁴⁾.

Clinical Evaluation

Initial physical examination, laboratory findings, and prognosis were reviewed using the descriptions provided by the collaborating institutes. Extranodal invasion by the lymphoma was confirmed by the biopsy examination. Kaplan-Meier actuarial estimates of overall survival were compared using the log-rank analysis.

Result

Histologic Findings, Enzyme, and Histochemical Analysis of mantle cell lymphoma

Histologic, enzyme and histochemical studies of lymphoma cells in mantle cell lymphoma are summarized in Table 2. Lymphoma cells in all the mantle cell lymphoma cases were positive for CD19 (B4) and CD20 (B1). Examined mantle cell lymphoma showed SIgM lambda (6 cases), M kappa (4), MD lambda (4), MD kappa (3), MDA kappa (2), MA lambda (one), and MDG kappa (one). No expression of CD10 and CD11c was found in the cases of mantle cell lymphoma. Examined cases of mantle cell lymphoma were classified into 4 groups according to the cell surface

Table 1. Panel of antibodies and single enzyme used

Reagent	CD no.	Source
B4	19	Coulter
B1	20	Coulter
Immunoglobulin M, D, G, A Kappa, lambda		Dako
Leul	5	Becton Dickinson
Anti-Tac (Anti-interleukin 2 α receptor)	25	Dr. T. Uchiyama
CALLA	10	Coulter
LeuM5	11c	Becton Dickinson
Ki-Mlp		Dr. M. R. Parwaresch
Anti-PCNA/cylin		Dako
OKT 11	2	Coulter
Anti-DRC		Dako
S100 protein		Dako
Alpha-1 antichymotrypsin		Dako
Lysozyme		Coulter
Naphthol AS-BI phosphate		Sigma

DRC: dendritic reticulum cell;

CALLA: common acute lymphocytic leukemia antigen;

PCNA: proliferating cell nuclear antigen.

Table 2. Histologic, enzyme, and immunohistochemical findings, and proliferation rate of nucleated cells, reactive cells, and vascular reaction in mantle cell lymphoma

Case no.	NC	PF	Slg	Clg	CD25 IL-2R	CD5 Leu1	ALP-ase	CD10 CALLA	CD11c LeuM5	Ki-67 M1P	PCNA /c(%)	DRC	IDC 10 ³ /μm	His 10 ³ /μm	Vas. React.
Group A															
1	I>L,R	+	MK	-	+	+	-	-	-	+	22	+	4	21.3	+
2	I	+	MDAK	-	+	+	-	-	-	-	16	++	11	13.3	++
3	I=R	+	MDL	-	+	+	-	-	-	-	8	++	6.7	6.7	+
4	I=R	+	MDL	-	+	+	-	-	-	-	18	++	6.7	6.7	++
5	I	+	ML	-	+	+	-	-	-	-	13	+	2.7	12	+
6	I=R	+	MDK	-	+	+	-	-	-	-	14	++	4	6.7	++
7	I=R	+	MDL	-	+	+	-	-	-	+	8	++	6.7	4	++
8	I=R	-	MDL	-	+	-	-	-	-	-	13	+	11	30	+
Group B															
9	I>R	-	MAL	-	-	+	-	-	-	-	12	++	27	56	+
10	I>R	+	MDAK	-	-	+	-	-	-	-	12	++	4	13.3	+
11	I>R	+	ML	-	-	+	-	-	-	-	21	+	4	26.7	+
12	I>R	-	ML	-	-	+	-	-	-	-	31	++	15	43.3	++
13	I>R	-	MDK	-	-	+	-	-	-	+	26	+	2.7	21.3	+
14	I>R	-	ML	-	-	+	-	-	-	+	24	++	4	9.3	+
15	I	-	MK	-	-	+	-	-	-	+	12	-	9.3	9.3	+
Group C															
16	I	-	MK	-	-	-	-	-	-	-	27	++	4	6.7	+
17	I>R	-	MDGK	-	-	-	-	-	-	+	39	+	9.3	12.4	+
18	I=L	-	ML	-	-	-	-	-	-	-	14	++	2.7	18.7	+
Group D															
19	R>I	+	MK	-	-	-	+	-	-	+	39	++	67	80	++
20	R>I	+	MDK	-	-	-	+	-	-	-	26 ^ψ	++	51 ^ψ	83 ^ψ	++
21	R>I	+	ML	-	-	-	+	-	-	+	43	++	45	59.3	++

NC: nuclear configuration (R: round; I: indented; L: lobulated); PF: preserved follicles; his: histiocytes; Vas. React.: vascular reaction; ψ : significantly different from each group A, B, and C by Student's t-test ($p < 0.01$).

markers. Group A (8 cases) showed diffuse proliferation of CD25⁺, CD5⁺, and ALPase⁻ indented and/or round nuclear lymphoma cells and preserved germinal centers. The lymphoma cells in another 7 cases (group B) were positive for CD5, but negative for CD25 and ALPase. The lymphoma cells in the group B mainly had indented nuclei (Fig. 1). In 6 CD25⁻ and CD5⁻ cases of mantle cell lymphoma, the lymphoma cells in 3 cases (group C) were negative for ALPase, having indented nuclei. Lymphoma cells in the remaining 3 cases (group D) showed a positive reaction to ALPase. Group D cases were composed of mainly round nuclear lymphoid cells, and formed diffuse and zonal growth features in the mantle zone and paracortex (Figs. 2, 3, 4). A few atypical large lymphocytes were intermingled. Anti-PCNA/c⁺ cells in group D were significantly higher than those in the other mantle cell lymphoma groups ($p < 0.01$, t test). Anti-PCNA/c⁺ cells were located near the increased venules in the mantle zone and enlarged paracortex in group A (4 cases), group B (one) and group D (3). Irregular and delicate dendritic reticulum cells (DRCs) networks were distributed in 5 cases of group A, 4 of group B, 2 of group C, and all 3 of group D. Group D cases showed a significant increase of IDCs and histiocytes compared with other

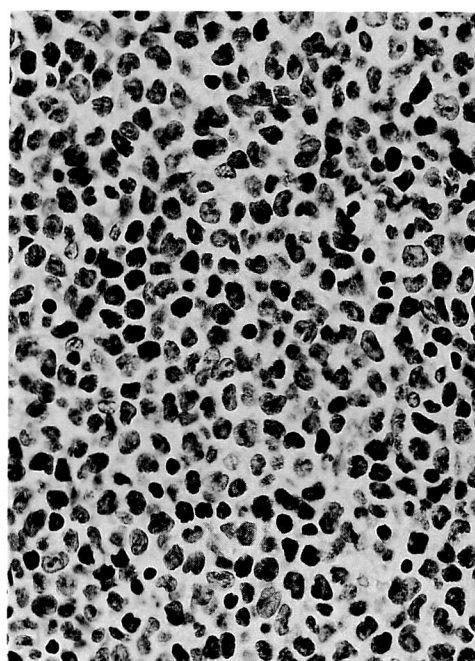


Fig.1. Diffuse infiltration of medium sized lymphoma cells with indented nuclei in mantle cell lymphoma group B. (H&E, X500)



Fig. 2. So-called marginal zone lymphoma. Case 20. Zonal proliferation of atypical lymphoid cells in outer mantle and paracortex, and a preserved lymph follicle in the upper left. (H&E, x170)

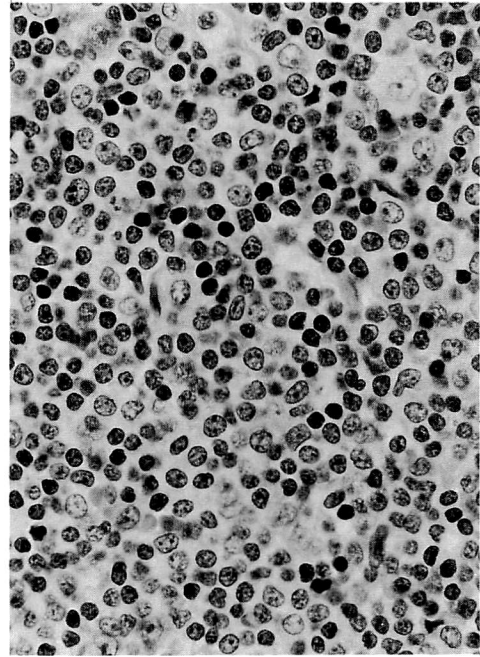


Fig. 3. Lymphoma cells of so-called marginal zone lymphoma have round nuclei and slightly coarse chromatin. A few atypical transformed lymphocytes are found. Case 20. (H&E, X500)

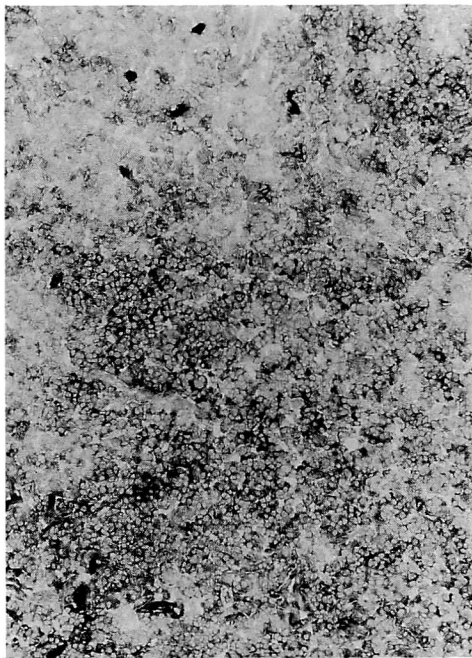


Fig. 4. Diffuse infiltration of alkaline phosphatase-positive lymphoid cells in so-called marginal zone lymphoma. Case 19. (X170)

groups in mantle cell lymphoma ($p < 0.01$, t test).

Other Types of Examined Lymphomas

Table 3 summarizes the characteristics of lymphoma cells in B-CLL, immunocytoma, MBCL and centroblastic/centrocytic lymphoma. In 5 cases of B-CLL, the lymphoma cells with round and/or indented nuclei showed SIgM⁺D⁺, CD5⁺, CD25⁺, ALPase⁻, CD10⁻, and CD11c⁻. B-CLL showed prominent histiocytic reaction compared with each group A, B, and C of mantle cell lymphoma ($p < 0.01$, t test). The phenotype of the lymphoma cells in B-CLL was almost the same as that of mantle cell lymphoma group A. In 5 immunocytoma cases, scattered lymphoplasmacytic cells showed monoclonal cytoplasmic IgG (3 cases), IgM (one), and IgA (one), CD11c⁺(3), ALPase⁻, and CD10⁻. All the immunocytoma cases had small germinal centers, a significantly higher rate of anti-PCNA/c⁺ cells, and prominent histiocytic and IDCs infiltration compared with each group A, B, and C of mantle cell lymphoma ($p < 0.01$, t test). Lymphoma cells with clear cytoplasm in 4 MBCL cases showed SIgG⁺ (2 cases), and SIgM⁺ (one), CD11c⁺ (2), ALPase⁻, and CD10⁻ (Figs. 5, 6). Three of 4 MBCL cases showed CD25⁻ and CD5⁻.

Table 3. Histologic, enzyme, and immunohistologic findings, and proliferation rate of mononuclear cells, reactive cells, and vascular reaction

Case no.	NC	PF	Slg	Clg	CD25 Tac	CD5 Leu1	ALP-ase	CD10 CALLA	CD11c LeuM5	Ki-67 M1P	PCNA /c(%)	DRC	IDC 10 ³ /μm	His	Vas. React.
B-chronic lymphocytic leukemia															
1	I>R	-	MK	-	+	+	-	-	-	-	20	++	6.7	12	+
2	R	-	MDL	-	+	+	-	-	-	-	26	++	6.7	53.3	+
3	I>R	+	MDL	-	+	+	-	-	-	-	24	+	5.3	58 ψ	+
4	R	-	K	-	-	+	-	-	-	-	12	+	4	43	+
5	I>R	-	ML	-	+	+	-	-	-	-	45	++	12	74.5	+
Lymphoplasmacytic/-cytoid lymphoma															
1*	R	+	MK	MK	-	+	-	-	+	-	48	+	37	159	++
2	I>R	+	-	AK	+	+	-	-	-	-	47	+	27	111	++
3*	R	+	-	GK	-	-	-	-	+	-	70 ψ	+	85 ψ	86.3 ψ	++
4	R	+	DK	GK	-	-	-	-	+	-	67	-	96	120	++
5	R	+	-	GL	-	-	-	-	-	-	29	+	57	73.3	++
Monocytoid B cell lymphoma															
1	R	+	GK	-	+	+	-	-	-	-	36	+	5.3	116	+
2	R	+	GL	-	-	+	-	-	+	+	29	+	19	49.6	++
3	R>I	+	MK	-	-	-	-	-	-	-	33 ψ	+	9.3	112 ψ	++
4	R	+	K	-	-	-	-	-	+	+	34	-	4	42.3	+
Diffuse, centroblastic/centrocytic lymphoma															
1	R>L	-	MK	-	-	-	-	+	-	-	49	+	24	42.3	++
2	I>R,L	-	MDK	-	-	-	-	+	-	-	57	++	6.7	49.7	++
3	L>R	-	MK	-	-	-	+	+	-	-	26	+	4	20.7	+
4	R=L	-	MDA	-	-	-	+	+	-	-	41 ψ	++	2.7	18.9 ψ	++
5	L	-	MDL	-	-	-	+	+	-	-	38	++	12	20.7	+
6	I>L	-	MDL	-	-	-	+	+	-	-	37	++	4.8	28.5	++
Follicular, centroblastic/centrocytic lymphoma															
1	L	-	ML	-	-	-	+	+	-	-	26	++	4	41.2	++
2	L	-	MGL	-	-	-	-	+	-	-	16	++	13	80	+
3	L>I	-	MK	-	-	-	-	+	-	-	22 ψ	++	2.7	64 ψ	+
4	L>I	-	MAK	-	-	-	-	+	-	-	53	++	6.7	13.3	+
5	L>R	-	MDL	-	-	-	+	+	-	-	22	+	7	52	+

*: lymphoma cells are negative for CD19 (B4) and CD20 (B1); NC: nuclear configuration (R: round; I: indented; L: lobulated); PF: preserved follicles; His: histiocytes; Vas. React.: Vascular reaction; ψ : significantly different from mantle cell lymphoma group A, B, and C by Student's t test ($p < 0.01$).

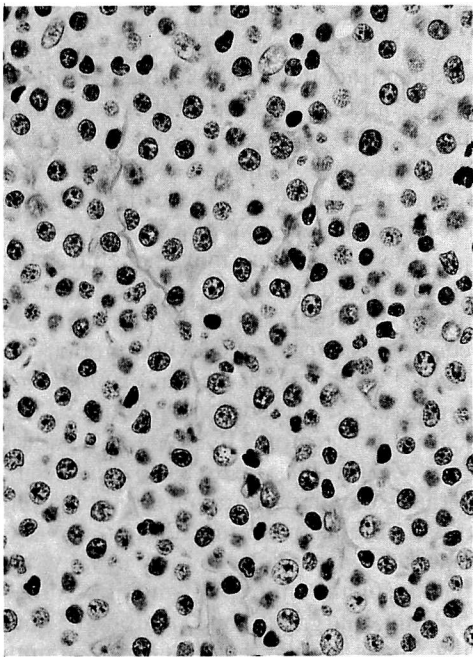


Fig.5. Monocytoid B cell lymphoma. Case 2. Lymphoma cells show round small and medium-sized nuclei and abundant clear cytoplasm. (H&E, X500)

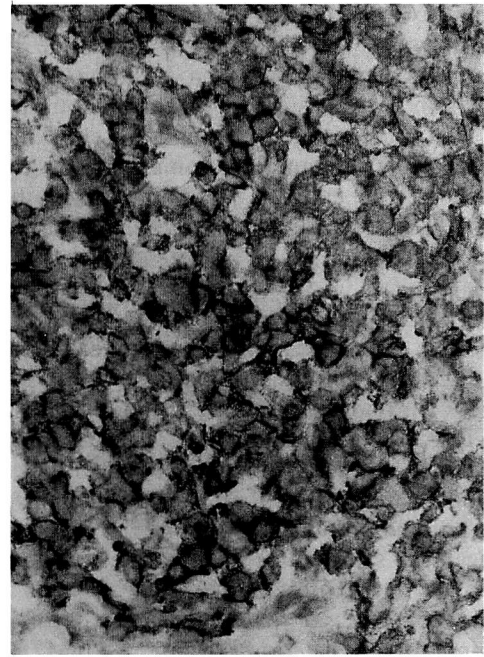


Fig.6. Monocytoid B-cell lymphoma. Case 2. Positive reaction for CD11c in the abundant cytoplasm. (ABC-alkaline phosphatase, X500)

Examined MBCL cases showed a significantly higher anti-PCNA/c⁺ rate, and histiocytic reaction in comparison with each group A, B, and C of mantle cell lymphoma ($p < 0.01$, t test). Diffuse centroblastic/centrocytic lymphoma in 6 cases showed SIgM⁺ or SIgM⁺D⁺, CD10⁺, CD25⁻, CD5⁻, and CD11⁻, in which that of 4 cases had ALPase activity.

Chinical Aspects

All 8 cases of mantle cell lymphoma group A showed bone marrow invasion by the lymphoma cells with peritrabecular patchy and nodular growth patterns, but revealed neither lymphocytosis nor leukemic changes. Three cases of mantle cell lymphoma group A showed an involvement by the lymphoma cells in the gastrointestinal mucosa. Invasion by lymphoma cells in the lung and spleen occurred in 2 cases of group A. Of the 6 cases in the mantle cell lymphoma group B, 2 showed extranodal involvement in the bone marrow, 2 in the gastrointestinal tract, and one each in the orbit, skin, and retroperitoneum. Two cases of mantle cell lymphoma group C showed an involvement in the stomach or pharynx. In mantle cell lymphoma group D, systemic and localized superficial lymphadenopathy was found in each case, but no abdominal lymphadenopathy was noted. Dermal invasion by the lymphoma cells and splenomegaly were detected in each one case of mantle cell lymphoma group D, while no involvement by the lymphoma was found in the gastrointestinal tract, salivary gland and bone marrow. No leukemic changes were found during the clinical course of the cases of mantle cell lymphoma group D. In the 4 cases of MBCL, splenomegaly was detected in 3 cases and swollen salivary glands in 2 cases. Abdominal lymphadenopathy was found in 3 MBCL cases. One case of MBCL showed leukemic changes and bone marrow involvement by the lymphoma cell. No significant differences in overall survival could be found among patients in each examined mantle cell lymphoma group, B-CLL, immunocytoma, MBCL, and centroblastic/centrocytic lymphoma cases by the Kaplan-Meier method and log-rank analysis.

Discussion

Lymphoma cells in examined mantle cell lymphoma cases showed almost the same characteristics of SIgM⁺ and CD10⁻ lymphocytes with or without expression of SIgD, CD25, CD5, and ALPase. These lymphocytes are located in the primary lymph follicles and interfollicular area rather than in the follicular center. Mantle cell lymphoma frequently expressed CD5 antigen, while a small number of mantle cell lymphoma cases showed no expression of CD5^{2,4,15}. Van den Oord and colleagues¹¹ presented 7 cases of mantle zone lymphoma consisted of ALPase⁺, SIgM⁺ CD5⁻, and CD10⁻ lymphoma cells. These cases showed zonal infiltration of mainly round nuclear lymphoma cells

around well-developed lymph follicles. They suggested that the mantle zone lymphoma was derived from marginal zone lymphocytes. In examined 6 cases of CD5⁻ mantle cell lymphoma, we found 3 cases of SIgM⁺, ALPase⁺ lymphoma, having similar histologic and phenotypic findings of marginal zone lymphocytes. These 3 cases showed zonal proliferation of round nuclear lymphoma cells with the same phenotype as marginal zone lymphocytes in the irregular DRCs networks, together with many IDCs and histiocytes. The cytologic and histologic findings in mantle cell lymphoma group D were different from the other groups of mantle cell lymphoma and the other types of low-grade B cell lymphoma. From these findings, we strongly suggest that the mantle cell lymphoma of the 3 patients in group D is the neoplastic counterpart of marginal zone lymphocytes. Hence we suggest ALPase⁺, CD5⁻, and CD10⁻ medium-sized lymphoma with interfollicular growth pattern be termed so-called marginal zone lymphoma.

On the other hand, since MBCL is distributed in the perifollicular area of the lymph node and mucosa associated lymphoid tissue (MALT), Piris¹⁶) and Nizze¹⁷) suggested that MBCL was derived from marginal zone lymphocytes. In examined cases, MBCL had different cell markers about IgG, and CD11c, and less DRCs networks and IDCs reaction than those of so-called marginal zone lymphoma. Further, the immunophenotypes of MBCL are different from those of marginal zone lymphocytes. Clinically, MBCL frequently involves the salivary glands, gastrointestinal tract and spleen¹⁸). Cases of MBCL also occasionally complicate Sjögren syndrome. In examined cases of so-called marginal zone lymphoma, superficial lymphadenopathy is a typical clinical feature. No tumor invasion was detected in the salivary gland and gastrointestinal tract during the whole clinical course of the 3 cases. From this, we suspect that the clinicopathologic features of MBCL are different from those of so-called marginal zone lymphoma. MBCL might have similar cell markers of IgG, CD11c and DRCs reaction to those of immunocytoma¹⁹).

In the 3 cases of so-called marginal zone lymphoma, a few atypical large lymphocytes were intermingled. This kind of lymphoma should be differentiated from diffuse centroblastic/centrocytic lymphoma. So-called marginal zone lymphoma showed interfollicular growth pattern and some scattered S100 positive IDCs in the involved site. Furthermore, this type of lymphoma was negative for CD10. This leads us to believe it is very doubtful that so-called marginal zone lymphoma is derived from follicular center cells.

Marginal zone lymphocytes are usually found in Peyer's patch, splenic white pulp and abdominal lymph nodes. Splenic marginal zone lymphoma has been reported, to have similar histologic and immunophenotypic findings to marginal zone lymphocytes²⁰). Clinicopathologic and cytogenetic studies are necessary

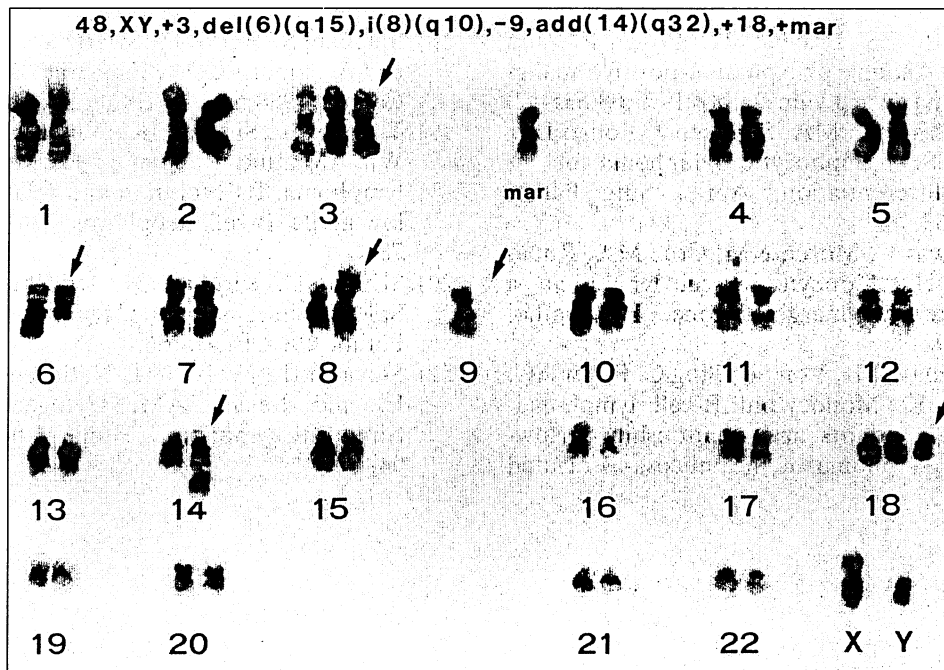


Fig.7. A karyotype from Case 20 of so-called marginal zone lymphoma. Stemline: 48, XY, +3, del (6)(q15), i(8)(q10), -9, add (14)(q32), +18, +mar.

to confirm whether marginal zone lymphoma and MBCL should be classified as the same disease entity. We examined the cytogenetic study in one case of so-called marginal zone lymphoma (unpublished data). The designation of the stemline was 48, XY, +3, del (6)(q15),i(8)(q10),-9,add(14)(q32), +18, +mar (Fig. 7). No aberrations of the *bcl-1* and *bcl-2* oncogenes' loci were detected. There was no report about chromosomal abnormality in MBCL²¹). Further cytogenetic study is necessary to confirm that marginal zone lymphoma is a distinct disease entity.

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