J Clin Exp Hematop
Vol. 56, No. 1, June 2016

Case Study

Composite Follicular Lymphoma and CD5-Positive Nodal Marginal Zone Lymphoma

Masashi Miyaoka,[1)] Tomoki Kikuchi,[1)] Joaquim Carreras,[1)] Yukie Yara Kikuti,[1)] Ken Omachi,[2)] Minoru Kojima,[2)] Kiyoshi Ando,[2)] and Naoya Nakamura[1)]

Composite CD10-positive low-grade B-cell and CD5-positive low-grade B-cell lymphoma is extremely rare. We report a case of a composite follicular lymphoma (FL) and CD5-positive nodal marginal zone lymphoma (NMZL) in a resected inguinal lymph node of a 72-year-old Japanese male. Histologically, multiple follicles had reactive-germinal centers with tingible body macrophages, a thin mantle zone and a wide marginal zone. The wide marginal zone consisted of medium-sized cells having slightly indented nuclei and clear cytoplasm, indicating monocytoid cells with CD5-positive B-cells. Several follicles had germinal centers filled with many centrocytes, with CD10-positive B-cells. Polymerase chain reaction/sequence analysis of the immunoglobulin heavy chain gene obtained from microdissected regions of CD5-positive NMZL and FL showed different sequences within the CDR3 region. To our knowledge, this is the first report of FL and CD5-positive NMZL. 〔*J Clin Exp Hematop 56(1):55-58, 2016*〕

Keywords: composite lymphoma, follicular lymphoma, CD5-positive nodal marginal zone lymphoma

INTRODUCTION

Composite lymphoma (CL) is defined as two histologically distinct variants of malignant lymphoma occurring in the same organ or mass.[1,2] CL is quite rare, with frequency ranging from 1 to 4.7% of lymphoma cases.[3] Many combinations of lymphoma types have been reported in CLs, including composite B-cell lymphoma, composite B- and T-cell lymphoma, and composite Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[2] Previously reported cases of composite HL and NHL were combinations of HL and B-cell non-Hodgkin lymphoma, such as HL and follicular lymphoma (FL), as well as HL and diffuse large B-cell lymphoma.[4-6] In some cases, polymerase chain reaction (PCR) amplification and sequence analysis of the immunoglobulin heavy chain gene (IGH) demonstrated common clonal origins in the two abovementioned cases,[5,6] suggesting the clonal relationship in combination HL and NHL.

Received: November 16, 2015
Revised : December 5, 2015
Accepted: January 7, 2016
[1)]Department of Pathology and [2)]Division of Hematology/Oncology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan
Corresponding author: Masashi Miyaoka, M.D., Department of Pathology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan
E-mail: miyaokamasasi828@yahoo.co.jp

Several combinations of low grade B-cell lymphoma, including FL and mantle cell lymphoma (MCL), FL and B-chronic lymphocytic leukemia/small lymphocytic lymphoma, and MCL and nodal marginal zone lymphoma (NMZL), have also been reported.[7-9] Some of these cases showed clonal relation whereas other cases were clonally unrelated.[7-9]

We report a case of CL of FL and CD5-positive NMZL in a lymph node, and demonstrated different B-cell clones in the FL and CD5-positive NMZL.

CASE REPORT

A 72-year-old, Japanese male had been treated for hypertension and suspicion of Parkinson's disease by his family doctor. The patient noticed a mass in the left groin one year prior. The mass was small, and the patient did not have fever or any other symptoms. After 6 months, the size of the mass began to increase. His family doctor then referred him to a hematologist at our hospital, and masses were identified in the left groin, right neck, and left flank. Excisional biopsy of an inguinal lymph node was performed for pathological diagnosis with flow cytometry and karyotype analyses. Peripheral blood evaluation revealed a hemoglobin level of 13.0 g/dL, a platelet count of 13.7 x 10^4/μL, a white blood cell count of 5.0 x 10^3/μL, LD 155 U/L, and soluble interleukin-2 receptor of 2,380 U/L. Positron emission tomography

showed abnormal accumulation in the right neck, right clavicles, para-aorta, left ilium, and left groin. Flow cytometry demonstrated predominant B-cells, and $CD19^{+}CD5^{+}$ and $CD20^{+}CD10^{+}$ fractions were observed. No restriction of the light chain (κ/λ) was observed, which may have been due to the $CD20^{+}CD10^{+}$ fraction involving neoplastic and reactive cells.

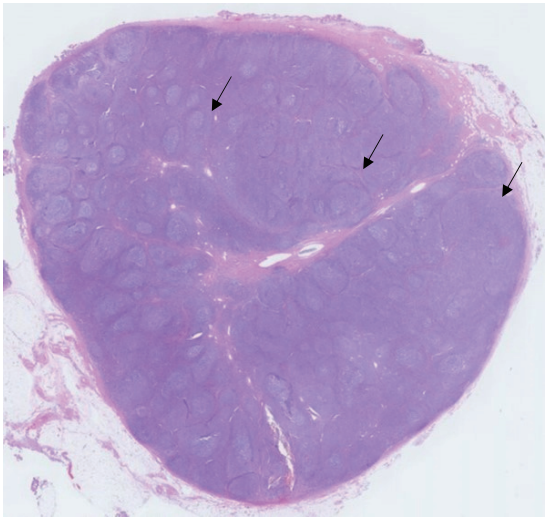

Fig. 1. Low power view of resected lymph node. Many follicles are distributed throughout the lymph node. Most follicles show marginal zone lymphoma, but several follicles show follicular lymphoma (*arrows*). H&E stain.

The patient's karyotype was normal, 46/XY[20/20]. Bone marrow involvement was not observed by histology and immunohistochemistry evaluation of the clot section. Low grade B-cell lymphoma was diagnosed. The patient underwent R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy and achieved remission.

PATHOLOGICAL FINDINGS

Histological evaluation of the resected lymph node demonstrated multiple follicles evenly distributed throughout (Fig. 1). Most follicles had a reactive-germinal center (GC) with tingible body macrophages, thin mantle zone, and wide marginal zone (Fig. 2). The wide marginal zone consisted of medium-sized cells having a slightly indented nucleus and clear cytoplasm, indicating monocytoid cells (Fig. 2). There were several follicles that had GCs filled with numerous centrocytes (Figs.1 & 2). Plasma cell differentiation was unclear in both the wide marginal zone and centrocyte-rich GC.

Immunohistochemically, monocytoid cells in the wide marginal zone were $CD3^{-}$, $CD5^{+}$, $CD10^{-}$, $CD20^{+}$, $BCL\text{-}2^{+}$, $BCL\text{-}6^{-}$, $MUM\text{-}1^{-}$ and cyclin $D1^{-}$, and lymphocytes in the GC

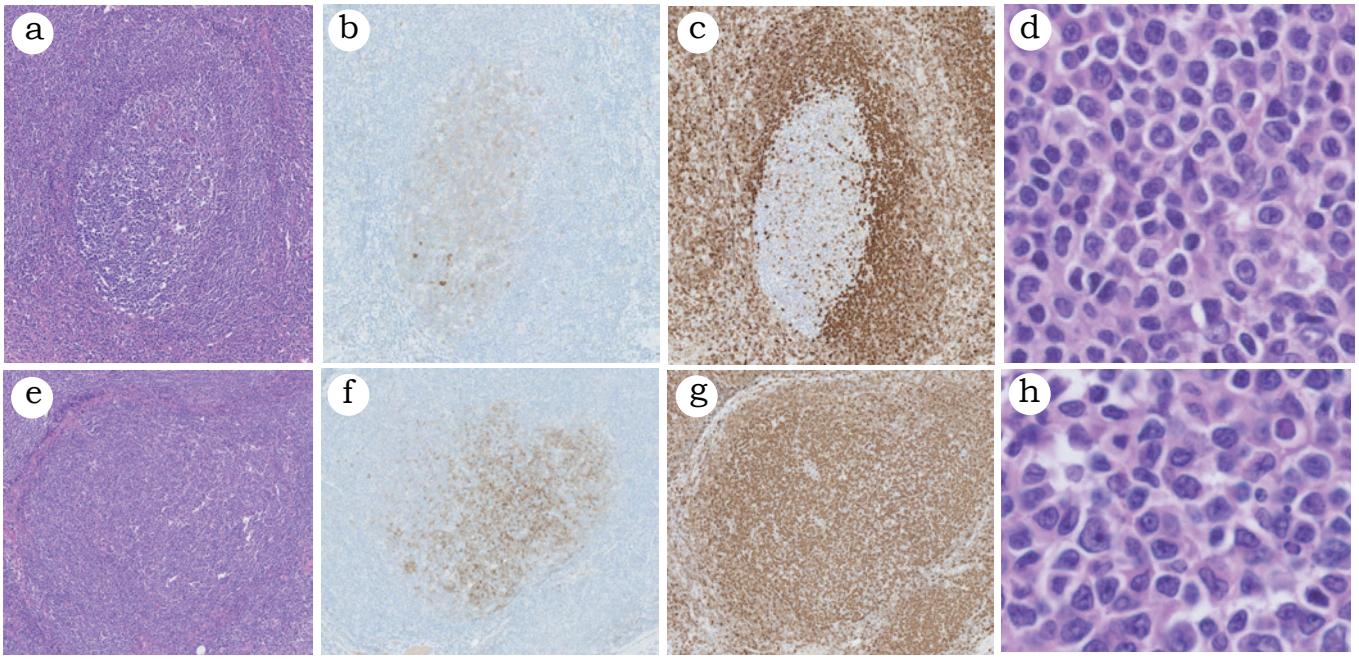

Fig. 2. Histopathology and immunohistochemistry of marginal zone lymphoma and follicular lymphoma. Nodal marginal zone lymphoma show a wide marginal zone (MgZ), mantle zone (MZ) and germinal center (GC)(***2a***). CD10 positivity is observed in the GC, but not the MgZ (***2b***), and BCL-2 positivity is observed in the MgZ and MZ, but not the GC (***2c***). Under high power view, the MgZ consists medium-sized cells having slightly indented nuclei and clear cytoplasm, indicating monocytoid cells (***2d***). Follicular lymphoma shows GC swelling (***2e***). Both CD10 and BCL-2 positivity is observed in the GC (***2f, 2g***). Under high power view, the GC consisted of small cleaved cells (***2h***). (*2a*), (*2d*), (*2e*) & (*2h*), H&E stain.

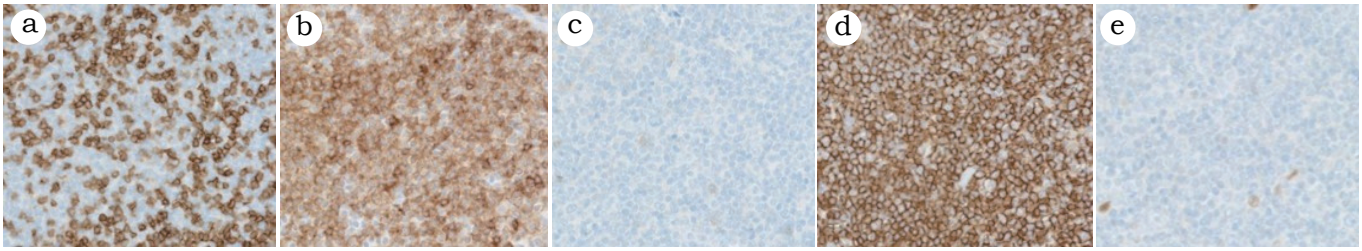

Fig. 3. Immunohistochemistry of nodal marginal zone lymphoma. Marginal zone cells were CD3-negative (***3a***), CD5-positive (***3b***), CD10-negative (***3c***), CD20-positive (***3d***), and Cyclin D1-negative (***3e***).

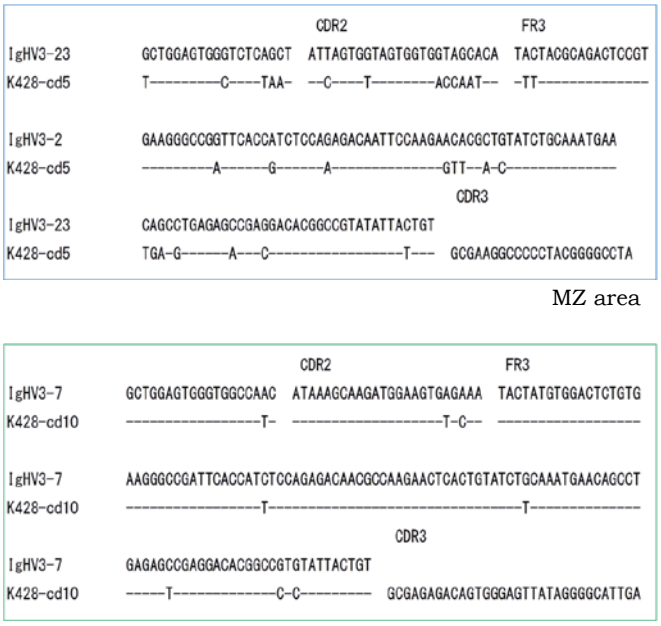

Fig. 4. Nucleotide sequence of the immunoglobulin heavy chain gene (IGH). Polymerase chain reaction and sequencing of IGH demonstrated that the marginal zone and centrocyte-rich germinal center had different sequences in the complementary determining region (CDR) 2, flame work region (FR) 3, and CDR3. Differences in the CDR3 indicate that these were two different clones.

were CD10$^+$ (weak), CD20$^+$, and BCL-2$^-$ (Figs. 2 & 3). These findings indicated CD5-positive NMZL. On the other hand, centrocytes in the GC were CD3$^-$, CD5$^+$, CD10$^+$, CD20$^+$, BCL-2$^+$, BCL-6$^+$, MUM-1$^-$, and cyclin D1$^-$, indicate FL (Fig. 2). Both κ^+ plasma cells and λ^+ plasma cells were observed in *in situ* hybridization, showing no restriction of the light chain.

PCR sequencing of the IGH from microdissected samples of the CD5-positive NMZL and FL showed different sequences in the CDR3 region, with IGHV3-23 in the CD5-positive NMZL and IgHV3-7 in the FL (Fig. 4).

DISCUSSION

We presented an unusual variation of CL composed of CD10-positive FL and CD5-positive NMZL, which to the best of our knowledge is the first case of such combination. Considering the results from the histological and immunohistochemical analysis, three possibilities were raised; (1) FL with marginal zone differentiation and CD5 expression, (2) CD5-positive NMZL with follicular colonization, or (3) composite lymphoma of FL and CD5-positive NMZL. Clarification of the clonal relationship is important in CL, and it is recommended to use not only morphological and immunohistochemical techniques, but also Southern blotting or PCR sequencing of the IGH and T cell receptor gene rearrangements, cytogenetics, and fluorescence *in situ* hybridization (FISH). In our case, PCR and sequence analysis of IGH demonstrated the different clones of the FL and CD5-positive NMZL.

Cases of CL containing a CD5-positive low grade B-lymphoma component have been previously reported.[7,8,10] In four of these cases, PCR sequencing of IGH was performed;[7,8] three of the cases showed common clonal origin and the other case had different clonal origins. Although the progenitor cells of CL containing CD5-positive low grade B-lymphoma with common clonal origin may be lymphoid stem cells or immature B-cells, the latter case and our case may have developed by chance.

MCL and chronic lymphocytic leukemia/small lymphocytic lymphoma are the main components observed in CL, and there has been a previously reported case of CL composed of CD5-positive splenic marginal zone lymphoma and FL with uncertain clonal relationship.[10] Due to the small number of cases, we were unable to determine the factor leading to the pathogenesis of CL composed of CD10-positive FL and CD5-positive low grade B-cell lymphoma, including MZL. Although such cases occur by chance, further accumulation of cases is important for identification of the factors involved in the pathogenesis of CL composed of FL and CD5-positive NMZL, as well as other CL.

In our case, the FL area was small, suggesting possible *in situ* FL. *In situ* FL has been recognized by the recent World Health Organization (WHO) classification system, but the incidence rate remains unknown due to the limited number of published cases and series.[11,12] *In situ* FL shows preservation of the nodal architecture, and most follicles appear to be

cytologically reactive, whereas rare germinal centers appear to be monotonous and lack tingible body macrophages.[11] The later follicles show strongly positive staining for BCL-2 and CD10, whereas the majority of follicles in the same lymph node are negative for BCL-2. In most cases of FL, tumor cells involve the majority of the follicles and infiltrate into the inter-follicular region; however, in *in situ* FL, tumor cells involve only a few follicles, and do not infiltrate into the many remaining reactive follicles or the inter-follicular region. There is also a possibility of overt FL of the systemic lymph nodes.

NMZL is currently defined in the WHO classification as a primary nodal B-cell lymphoma that morphologically resembles extranodal or splenic MZL, but without evidence of extranodal or splenic disease.[13] NMZL is uncommon, accounting for less than 2% of all lymphomas.[13] Generally, NMZL do not express CD5, but a few have been shown to do so. CD5-positive NMZL have histologic and immunophenotypic features typical of NMZL in addition to the expression of CD5. Jaso *et al*. reported the proportion of CD5-positive NMZL to typical NMZL to be 8.6% (7/91 cases).[14] Of the CD5-positive NMZL patients, 86% (6/7 cases) showed lymphadenopathy above and below the diaphragm, 6 cases underwent bone marrow check, and all cases had bone marrow invasion.[14] In our case, lymphadenopathy above and below the diaphragm was observed, but not bone marrow invasion.

In NMZL, CD5 has been reported to be expressed in only 8.6% cases, and CD5 expression correlates with a higher frequency of dissemination and bone marrow invasion.[14] However, patients with CD5-positive NMZL generally have an indolent clinical course and excellent overall survival.[14] In our case, although bone marrow invasion was not observed, dissemination above and below the diaphragm was present. In CD5-positive NMZL, the mechanism of CD5 expression and progenitor identification remain unclear; however, CD5 expression in NMZL may be associated with wide dissemination.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Kim H, Hendrickson R, Dorfman RF: Composite lymphoma. Cancer 40:959-976, 1977

2 Kim H: Composite lymphoma and related disorders. Am J Clin Pathol 99:445-451, 1993

3 Thirumala S, Esposito M, Fuchs A: An unusual variant of composite lymphoma: a short case report and review of the literature. Arch Pathol Lab Med 124:1376-1378, 2000

4 Jaffe ES, Zarate-Osorno A, Kingma DW, Raffeld M, Medeiros LJ: The interrelationship between Hodgkin's disease and non-Hodgkin's lymphomas. Ann Oncol 5 (Suppl 1):7-11, 1994

5 Bellan C, Lazzi S, Zazzi M, Lalinga AV, Palummo N, *et al*.: Immunoglobulin gene rearrangement analysis in composite Hodgkin disease and large B-cell lymphoma: evidence for receptor revision of immunoglobulin heavy chain variable region genes in Hodgkin-Reed-Sternberg cells? Diagn Mol Pathol 11:2-8, 2002

6 Bräuninger A, Hansmann ML, Strickler JG, Dummer R, Burg G, *et al*.: Identification of common germinal-center B-cell precursors in two patients with both Hodgkin's disease and non-Hodgkin's lymphoma. N Engl J Med 340:1239-1247, 1999

7 Wang S, Tzankov A, Xu-Monette ZY, Hoeller S, Wang SA, *et al*.: Clonally related composite follicular lymphoma and mantle cell lymphoma with clinicopathologic features and biological implications. Hum Pathol 44:2658-2667, 2013

8 Boiocchi L, Witter RE, He B, Subramaniyam S, Mathew S, *et al*.: Composite chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular lymphoma are biclonal lymphomas: a report of two cases. Am J Clin Pathol 137:647-659, 2012

9 Rodig SJ, Healey BM, Pinkus GS, Kuo FC, Dal Cin P, *et al*.: Mantle cell lymphoma arising within primary nodal marginal zone lymphoma: a unique presentation of two uncommon B-cell lymphoproliferative disorders. Cancer Genet Cytogenet 171:44-51, 2006

10 Demurtas A, Aliberti S, Bonello L, Di Celle PF, Cavaliere C, *et al*.: Usefulness of multiparametric flow cytometry in detecting composite lymphoma: study of 17 cases in a 12-year period. Am J Clin Pathol 135:541-555, 2011

11 Carbone A, Gloghini A, Santoro A: *In situ* follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 30:1-7, 2012

12 Harris NL, Nathwani BN, Swerdlow SH, de Jong D, Jaffe ES, *et al*.: Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al*. (eds): World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.220-226, 2008

13 Campo E, Pileri SA, Jaffe ES, Müller-Hermelink HK, Nathwani BN. Nodal marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al*. (eds): World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.218-219, 2008

14 Jaso JM, Yin CC, Wang SA, Miranda RN, Jabcuga CE, *et al*.: Clinicopathologic features of CD5-positive nodal marginal zone lymphoma. Am J Clin Pathol 140:693-700, 2013