The Korean Journal of Pathology
2006; 40: 151-5

Follicular Lymphoma with Monoclonal Plasma Cell Differentiation
– A Case Report –

**Hyunchul Kim · Young Seok Lee
Jungwoo Choi · Aeree Kim
Bom Woo Yeom · Hankyeom Kim
Insun Kim**

Department of Pathology, Korea University Medical College, Seoul, Korea

Received : November 24, 2005
Accepted : February 21, 2006

Corresponding Author
Insun Kim, M.D.
Department of Pathology, Korea University Guro Hospital, 80 Guro-dong, Guro-gu, Seoul 152-703, Korea
Tel: 02-818-6871
Fax: 02-818-6239
E-mail: iskim@korea.ac.kr

We present a case of recurrent follicular lymphoma with an extensive plasma cell component involving infra-auricular lymph nodes in a 64 year-old woman. Immunohistochemical staining showed a strongly positive reaction of the follicles with CD20, bcl-2, bcl-6, CD10 and CD21 on the first biopsy specimen. The intrafollicular and interfollicular plasma cells showed monoclonality for IgG heavy chain and lambda light chain. The histological and immunohistochemical findings in the recurrent tumor were identical with those of the original. Discussion is focused on the importance of the differential diagnosis between reactive lymphoid hyperplasia and other lymphomas having plasmacytic differentiation.

Key Words : Malignant lymphoma; Follicular lymphoma; Plasma cells

In lymph nodes, plasma cells are found in association with various disorders including rheumatoid arthritis,[1] Sjogren's syndrome,[2] syphilis,[3] Castleman's disease[4] and Hodgkin's and non-Hodgkin's lymphomas. Primary extramedullary plasmacytomas are also known to occur in lymph nodes.[5] Mature plasma cells and plasmacytoid lymphocytes are constituents of lymphoplasmacytic lymphoma, low-grade marginal zone B cell lymphoma and small lymphocytic lymphoma.[6,7] However, follicular plasma cells are found more frequently in follicular hyperplasia than in follicular lymphoma.[8] About twenty years ago, several reports described follicular lymphomas containing polyclonal or monoclonal plasma cell populations.[9-11] According to the review of Frizzera *et al*.,[12] follicular lymphoma with plasmacytic differentiation should be considered as a malignant lymphoma of intermediate grade, with no significant difference in patient survival or clinical findings when compared to lymphoplasmacytic lymphoma. We report here the histological and immunohistochemical findings in a case of a recurrent follicular lymphoma with monoclonal plasma cell differentiation. The differential diagnosis of lymph node lesions containing plasma cells is discussed in detail.

CASE HISTORY

A 64 year-old woman presented to the hospital complaining of a palpable mass in the left posterior cervical region. The mass was resected. Following a diagnosis of reactive lymphoid hyperplasia, she was sent home with no further treatment. Four years later, the patient revisited the hospital for evaluation of enlarged lymph nodes beneath the left ear. She had been aware of them for 7 months. On computerized tomography, several variable sized, enlarged, round lymph nodes were found on the left side at level II and within the left parotid gland. There were no cystic changes or calcification. Excision of the lymph nodes and the parotid gland was performed. Results of hematologic and biochemical studies were within normal limits. Serum protein was 7.1 g/dL on the first visit and 6.8 g/dL on the second visit.

Pathologic findings

The initial excised lymph node consisted of a round, soft lymph node, measuring $2.0 \times 1.5 \times 1.2$ cm in dimension. On section, the cut surface showed a fish-flesh appearance. The second biop-

sy specimen, obtained 4 years later, consisted of several conglomerated lymph nodes and a portion of parotid gland, totally measuring 3.0×1.5×1.0 cm overall.

Histological findings

The initial lymph node showed markedly enlarged or anastomosing lymphoid follicles with residual normal lymphoid tissue at the periphery. The follicles were composed of small lymphoid cells with round nuclei and scanty cytoplasm, large centroblast-like cells and plasmacytoid cells (Fig. 1). Neither a zonal pattern nor tingible body macrophages were evident. Interfollicular areas also showed plasma cell infiltration, especially around blood vessels. The second biopsy showed a cluster of small lymph nodes. One of those lymph nodes had markedly enlarged lymphoid follicles, which were composed of cellular components basically identical with the initial biopsy (Fig. 2). The other lymph nodes exhibited a total effacement of nodal architecture with diffuse infiltration by small lymphocytes and marked stromal sclerosis. Occasional plasma cells were identified, and they also were infiltrating into the parenchyma of the surrounding parotid gland.

Immunohistochemical staining results

Immunohistochemical staining was done on the first and second biopsies. The cells within the enlarged follicular structures were strongly positive for CD20, bcl-2, bcl-6 and CD10 (Fig. 3A-C). Scattered CD68-positive macrophages were occasionally seen. CD3-positive T cells were found mainly around the follicles and interfollicular areas. VS38-positive plasma cells were seen within the follicles as well as in the interfollicular areas (Fig. 3D). The plasma cells showed lambda light chain monoclonality (Fig. 3E, F). Within the follicles, the Ki-67 label-

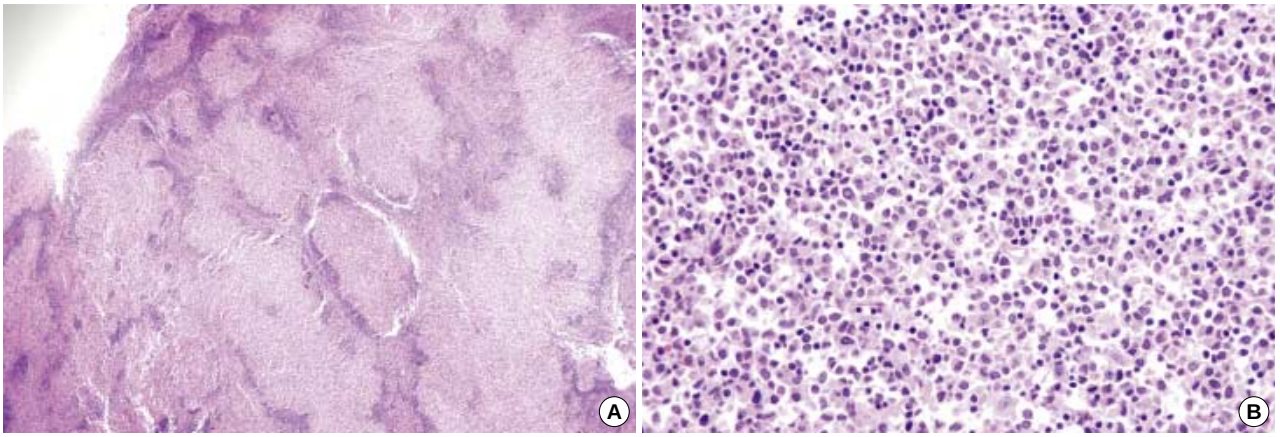

Fig. 1. The histology of the first lymph node biopsy. Germinal centers of follicles are expanded (A). The explanded germinal centers show mixed components of small lymphocytes, large centrocytes and centroblasts and plasma cells (B).

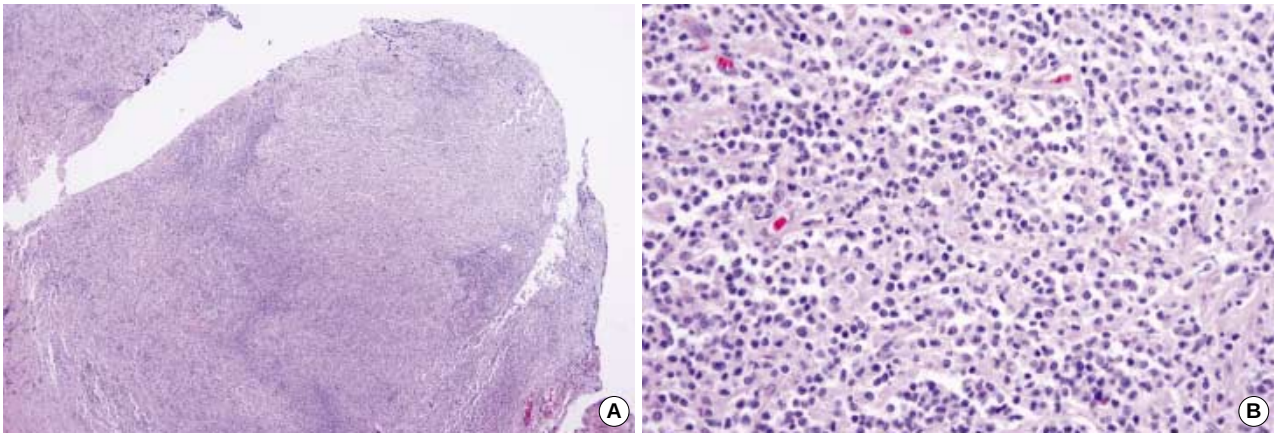

Fig. 2. The histology of lymph node of the second biopsy. An enlarged lymphoid follicle surrounded by residual rim of small lymphocytes is observed (A). Small and large lymphoid cells with plasma cells are found within the enlarged follicle (B).

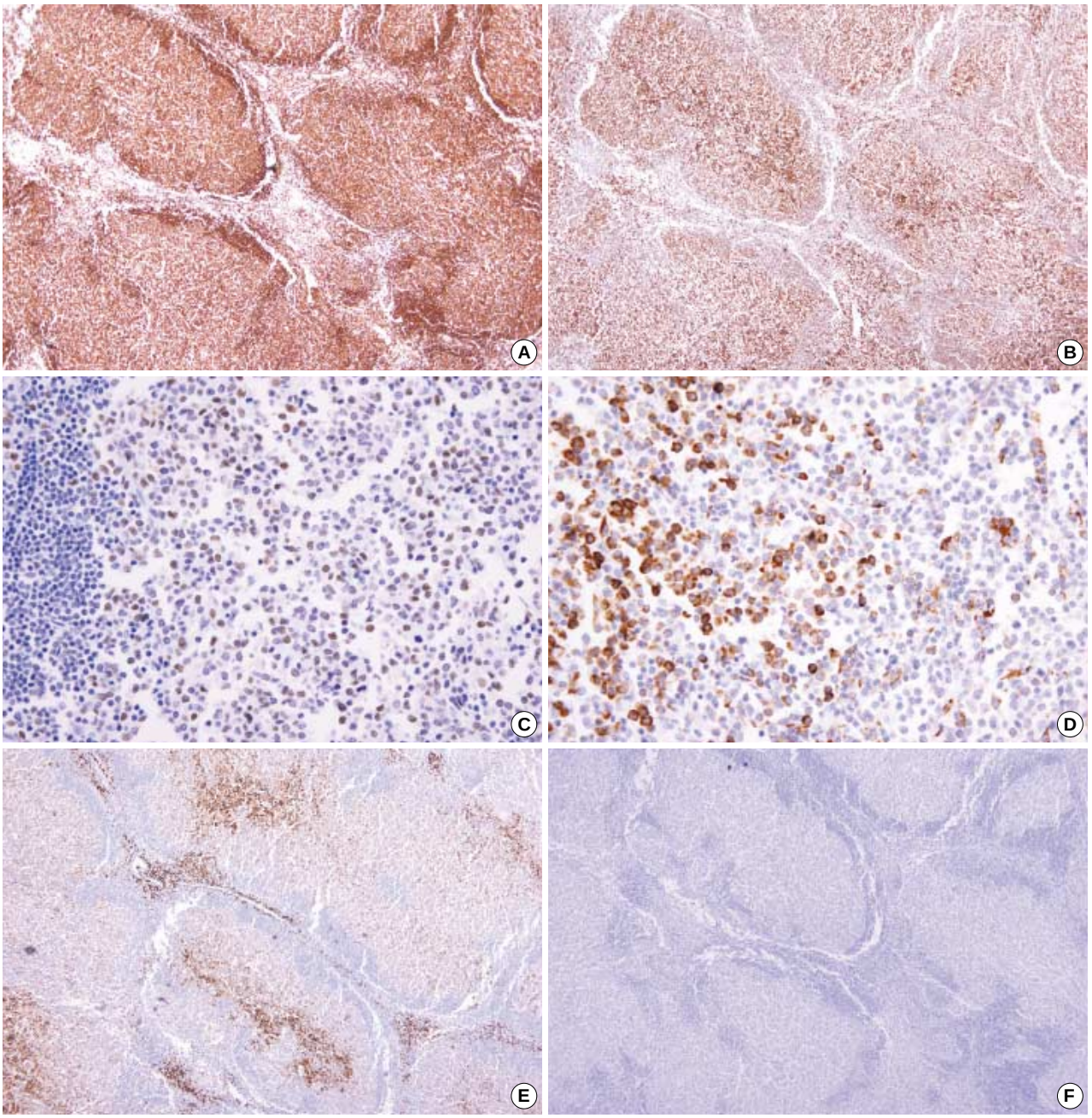

Fig. 3. The immunohistochemistry of the lymph node. The follicles are positive staining for CD20 (A), bcl-2 (B) and bcl-6 (C). The immunostaining for VS38a is positive in plamsma cells (D). The plasma cells within and outside the follicles are positive for lambda light chain (E), but negative for kappa light chain (F).

ing index was about 30%. The lymph nodes on the second biopsy, which showed diffuse sclerosis and infiltration of small lymphoid cells were composed of a mixed population of CD20-positive B cells and CD3-positive T cells, in equal proportion and in a haphazard fashion. Most of the cells were positive for bcl-2, but negative for bcl-6, CD10 and CD21. The area did not show lambda monoclonality.

DISCUSSION

Cases of follicular lymphomas with monoclonal plasma cells have been documented by Nemes *et al*.,[9] Schmid *et al*.[10] and Vago *et al*.[11] In 1986, Keith *et al*.[13] described 7 cases with plasmacytic differentiation from 198 follicular center cell lymphomas, and Frizzera *et al*.[12] reported 6 additional cases.

Follicular lymphomas, especially when showing plasmacytic differentiation should be differentiated from reactive follicular hyperplasia, which can be seen as a nonspecific B cell response to an immune stimulus or in association with rheumatoid arthritis, secondary syphilis or Castleman's disease.[1,3,4] Histologic findings such as a high density of follicles per unit area, even distribution of follicles between the cortex and medulla, and a relative paucity of mitotic figures and tingible body macrophages within the follicles help in differentiating follicular lymphoma from reactive hyperplasia. A positive reaction for bcl-2 antibody is another helpful diagnostic finding.[8]

Marginal zone lymphoma of the lymph node may be primary or secondary to extranodal or splenic marginal zone lymphoma.[7,14] The marginal zone and interfollicular areas of the lymph node are infiltrated by centrocyte-like B cells, monocytoid B cells or small B lymphocytes with scattered blasts. Follicular colonization may be present. Reactive non-neoplastic follicles are an important component of low grade marginal zone B cell lymphoma.[7] Isaacson *et al*.[14] described three types of follicle involvement by neoplastic cells (so called follicular colonization), which have a resemblance to follicular lymphoma. In the first type, reactive follicles are partially or completely replaced by centrocyte-like cells in which residual follicular center cells and mantle zone cells are dispersed. The neoplastic cells are CD10-negative, but bcl-2 protein-positive. In the second type, follicle centers are selectively replaced by centrocyte-like cells, which are larger in cell size and show higher rate of mitoses than seen in the diffuse infiltrates. Mantle zone and tingible body macrophages are present, but the zonal pattern of reactive follicle centers is lost. The neoplastic cells are CD10-negative and show markedly reduced expression of bcl-2. In the third type, the intrafollicular centrocyte-like cells show plasma cell differentiation. Immunophenotyping is essential for distinction between follicular lymphoma and neoplastic follicles in marginal zone B cell lymphoma. In follicular lymphoma, the follicles are CD10 and bcl-6-positive, and strongly express bcl-2 protein. In the present case, because the lymph nodes were found within and around the parotid gland, the secondary involvement of a salivary gland marginal zone lymphoma was strongly suspected. Based on the strong expressions of CD10, bcl-6, bcl-2 and CD21 in the follicles, follicular lymphoma was diagnosed.

Lymphoplasmacytic lymphoma is a rare neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving bone marrow, lymph nodes, spleen, or peripheral blood. Most cases previously diagnosed as lymphoplasmacytic lymphoma in extranodal sites are now reclassified as marginal zone B cell lymphoma of MALT.[15] The diagnosis of this type of lymphoma should be made after excluding small lymphocytic lymphoma, marginal zone B cell lymphoma and follicular lymphoma by morphologic and immunophenotypic findings. On immunohistochemical staining, the tumor cells show strong positive reaction for cytoplasmic immunoglobulin, usually IgM, B cell associated antigens and plasma cell antigen CD38, but with negative reactions for CD5, CD10 and CD23. Extra-osseous plasmacytoma may occur in lymph nodes.[7] However, these findings were not seen in the present case.

Frizzera *et al*.[12] reviewed the clinical and pathologic findings in 16 cases, which included the previously reported cases and their own 6 cases. A median survival of 3 years, a 22% rate of mortality, frequent extranodal involvement (44%), and the association with a monoclonal gammopathy were very similar findings to those of lymphoplasmacytic lymphoma, rather than follicular lymphoma.

Recently, Keller *et al*.[16] described one case of plasmacytic differentiation in 33 follicular lymphomas. Because the frequency of follicular lymphomas is low in Korea, compared to the Western countries,[17] the occurrence of plasmacytic differentiation in follicular lymphomas cannot be estimated.

REFERENCES

1. Nosanchuk JS, Schnitzer B. Follicular hyperplasia in lymph nodes from patients with rheumatoid arthritis. A clinicopathologic study. Cancer 1969; 24: 243-54.
2. Jaffe ES. Surgical pathology of the lymph nodes and related organs. 2nd ed. Philadelphia: WB Saunders, 1995; 100-1.
3. Hartsock RJ, Halling LW, King FM. Luetic lymphadenitis: a clinical and histologic study of 20 cases. Am J Clin Pathol 1970; 53: 304-14.
4. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972; 29: 670-83.
5. Lim YH, Park SK, Oh HS, *et al*. A case of primary plasmacytoma of lymph nodes. Korean J Intern Med 2005; 20: 183-6.
6. Pangalis GA, Nathwani BN, Rappaport H. Malignant lymphoma, well differentiated lymphocytic: its relationship with chronic lymphocytic leukemia and macroglobulinemia of Waldenstrom. Cancer 1977; 39: 999-1010.
7. Jaffe ES, Harris NL, Stein H, Vardiman JW, WHO classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC press, 2001; 149-50, 157-61.
8. Hicks EB, Rappaport H, Winter WJ. Follicular lymphoma; a re-eval-

uation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 1956; 9: 792-821.

9. Nemes Z, Thomazy V, Szeifert G. Follicular centre cell lymphoma with alpha heavy chain disease. A histopathological and immunohistological study. Virchows Arch A Pathol Anat Histol 1981; 394: 119-32.
10. Schmid U, Karow J, Lennert K. Follicular malignant non-Hodgkin's lymphoma with pronounced plasmacytic differentiation: a plasmacytoma-like lymphoma. Virchows Arch A Pathol Anat Histopathol 1985; 405: 473-81.
11. Vago JF, Hurtubise PE, Redden-Borowski MM, Martelo OJ, Swerdlow SH. Follicular center-cell lymphoma with plasmacytic differentiation, monoclonal paraprotein, and peripheral blood involvement. Recapitulation of normal B-cell development. Am J Surg Pathol 1985; 9: 764-70.
12. Frizzera G, Anaya JS, Banks PM. Neoplastic plasma cells in follicular lymphomas. Clinical and pathologic findings in six cases. Virchows Arch A Pathol Anat Histopathol 1986; 409: 149-62.
13. Keith TA, Cousar JB, Glick AD, Vogler LB, Collins RD. Plasmacytic differentiation in follicular center cell (FCC) lymphomas. Am J Clin Pathol 1985; 84: 283-90.
14. Isaacson PG, Norton AJ. Extranodal lymphomas. Edinburgh; New York: Churchill Livingstone, 1994; 28-32, 253-7.
15. Harris NL, Jaffe ES, Stein H, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361-92.
16. Keller C, Vankiani E, Murty V, Frizzera G, Alobeid B, Bhagat G. Comparison of morphology, grade, and cytogenetic abnormalities in t(14;18) and non-t(14;18) follicular lymphomas: Does anything correlate? (Abstract). Virchows Arch 2005; 447: 148.
17. Ko YH, Kim CW, Park CS, *et al*. REAL classification of malignant lymphomas in the Republic of Korea: incidence of recently recognized entities and changes in clinicopathologic features. Hematolymphoreticular Study Group of the Korean Society of Pathologists. Revised European-American lymphoma. Cancer 1998; 83: 806-12.