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Case Study

Different Histopathological Types of Orbital Lymphoma 16 Years after Systemic Follicular Lymphoma : Immunohistochemical and Immunogenetic Analyses of Two Cases

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The purpose of this study is to show that the histopathological type of an orbital lymphoma can differ from the systemic follicular lymphoma that precedes it. A 44-year-old man (Patient #1) and a 50-year-old man (Patient #2) presented with generalized lymphadenopathy due to grade 1 follicular lymphoma proven on lymph node biopsy. Patient #1 was followed without treatment for 16 years when he developed a right orbital mass. Patient #2 underwent several courses of combination chemotherapy as well as radiation but relapsed. The second biopsy of the lymph node nine years later showed the same histopathological type of follicular lymphoma. He developed an orbital mass on the right side 16 years after the initial presentation. In Patient #1, excisional biopsy of the orbital masses showed extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In Patient #2, biopsy revealed the orbital mass to be T-cell/histiocyte-rich diffuse large B-cell lymphoma. In Patient #1, when comparing the original lymph node biopsy to the orbital biopsy obtained years later, no evidence for clonality was noted by polymerase chain reaction. In Patient #2, the amplification by polymerase chain reaction of the immunoglobulin heavy chain gene rearrangement in the lymph node lesion and the orbital lesion gave rise to a single discrete band with the same DNA sequence except for five nucleotide changes, indicating the same clonality in the presence of genomic changes. In conclusion, orbital lymphomas can occur as a second lymphoma with a different histopathological type in the long-term follow-up of systemic lymphomas. The original and subsequent lymphomatous lesions may or may not share neoplastic cell clonality and all genomics. 〔*J Clin Exp Hematopathol 48(1) : 17-24, 2008*〕

Keywords: follicular lymphoma, MALT lymphoma, T-cell/histiocyte-rich diffuse large B-cell lymphoma, immunoglobulin heavy chain gene rearrangement, clonality

INTRODUCTION

Recent advances in diagnoses and treatment for malignancies including lymphomas have led to long-term survival of patients. Doctors have a better chance of encountering malignancy recurrence or relapse in the long-term follow-up of patients after successful treatment of the initial disease. In such circumstances, it becomes a problem whether the recurrence is the relapse of the original malignancy or a newly arised malignancy. In other words, the clonality of neoplastic cells between the original lesion and the recurrent lesion may or may not change.[1,2]

Malignant lymphomas have many different histopathological types according to the World Health Organization Classification of Tumors (Pathology and Genetics of Tumors of Hematopoietic and Lymphoid Tissues, IARC Press, Lyon, 2001). Main modalities of treatment are observation, chemotherapy and radiation. Survival rates differ among the histopathological types.[3,4] Case reports and case series have addressed the variable clonality of neoplastic cells in the recurrence of malignant lymphoma.[5-10] In this study, we present two patients who developed orbital lymphomas as different histopathological types 16 years after systemic follicular lymphoma, and we analyzed the clonalities of neoplas-

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tic cells between the original lesions and the recurrent lesions.

CASE REPORT

Patient #1

A 44-year-old man developed generalized lymphadenopathy including bilateral cervical, supraclavicular, axillary, and inguinal lymph nodes in March 1990. The left supraclavicular lymph node biopsy revealed follicular lymphoma, grade 1 (Fig. 1). He had no hepatosplenomegaly, mediastinal or abdominal lymphadenopathy. The patient chose observation as a treatment option. Systemic lymphadenopathy subsided gradually by the time of a 1997 follow-up.

In December 2000, the patient was found to have esophageal cancer (squamous cell carcinoma) and underwent esophagectomy and reconstruction with a gastric tube in January 2001. In May 2001, he had radiation, 60 Gy to the mediastinum and 46 Gy to the supraclavicular regions bilaterally. He had three courses of combination chemotherapy with 5-fluorouracil, cisplatin, and methotrexate over the ensuing year. Supplemental chemotherapy was added in 2003 and 2004.

In February 2006, the patient noted right exophthalmos where a mass was palpable in the upper orbital edge and the lesion was visible through the upper bulbar conjunctiva (Fig. 2). The best-corrected visual acuity was 1.2 in both eyes. The anterior segments and fundi of both eyes were normal. Magnetic resonance imaging demonstrated the mass extending from the orbital apex to the orbital edge superior to the globe (Fig. 2). Bone marrow biopsy revealed no malignancy and gallium scan showed no other abnormal uptake except for the orbital lesion. In March 2006, excisional biopsy through the conjunctiva was done under local anesthesia and showed extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (Fig.

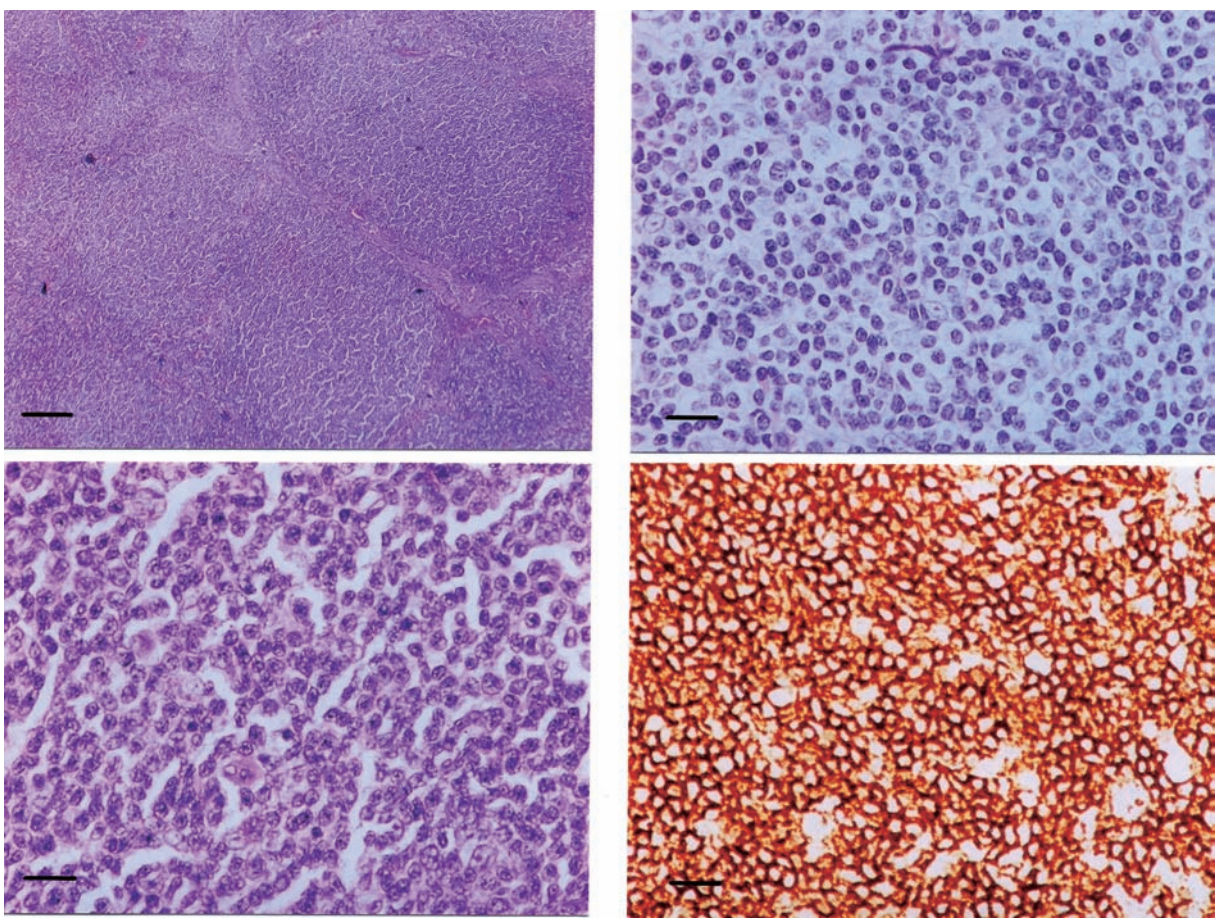


Fig. 1. Patient #1. Follicular lymphoma on supraclavicular lymph node biopsy in 1990 (*left column*) and MALT lymphoma on right orbital biopsy in 2006 (*right column*). Follicular growth pattern in a low magnification (*left top*) and a small number of centroblast-like cells in a high magnification (*left bottom*). Centrocyte-like cells and centroblast-like cells (*right top*) are positive to CD20 (*right bottom*). *Bar* = 200 μm in the left top panel and *bar* = 20 μm in the other panels.

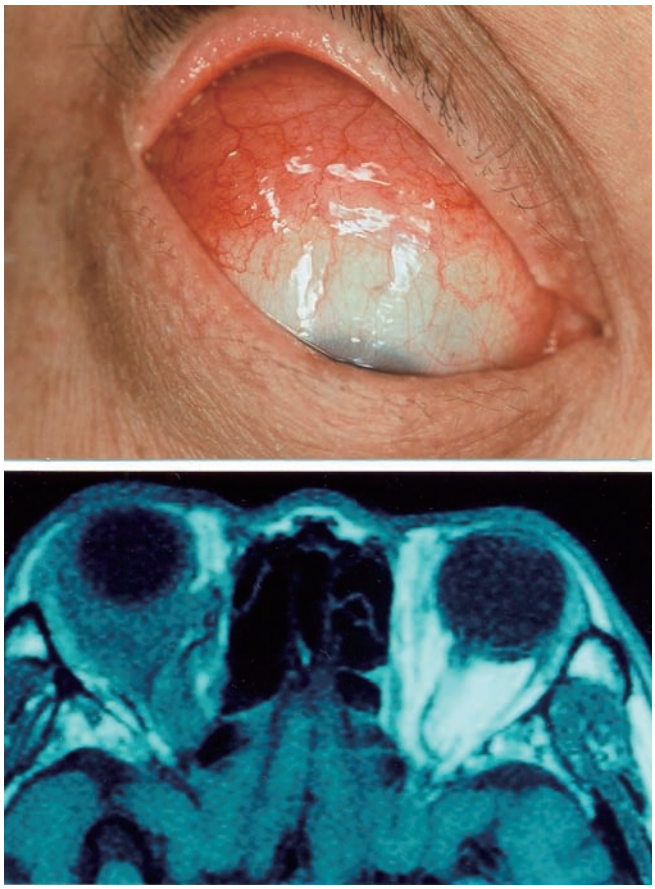


Fig. 2. Patient #1 in 2006. Orbital mass is visible as a salmon-pink lesion in the upper bulbar conjunctiva of the right eye (*top*) and a magnetic resonance image shows the mass extending from the orbital apex to the orbital edge superior to the right eye globe (*bottom*).

1). The patient then underwent radiation, 40 Gy, to orbital lesion.

Patient #2

A 50-year-old man developed generalized lymphadenopathy including bilateral axillary, inguinal, and paraaortic lymph nodes in July 1990. The right inguinal lymph node biopsy revealed grade 1 follicular lymphoma. The patient then underwent three courses of combination chemotherapy with vindesine sulfate, cyclophosphamide, and prednisolone. He was lost to follow-up for one and a half years until a reevaluation in March 1992 when he showed the recurrence of systemic lymphadenopathy including the involvement of bilateral axillary, inguinal, hilar and abdominal lymph nodes. From 1992 to 1993, the patient underwent several courses of combination chemotherapy : four courses of doxorubicin (adriamycin), cyclophosphamide, vindesine sulfate and prednisolone, five courses of etoposide, cyclophosphamide, mercaptopurine, procarbazine and prednisolone, and three courses of doxorubicin (adriamycin), cyclophosphamide, vindesine sulfate and prednisolone. In July 1993, the patient received 30 Gy of radiation to the paraaortic, pelvic, and bilateral inguinal regions. Twenty five Gy was administered to the mantle field, and 10 Gy was delivered to the right side of the neck. In 1999, the patient developed bilateral inguinal lymphadenopathy. The biopsy showed grade 1 follicular lymphoma (Fig. 3). He also showed the bone marrow involvement. No treatment was given during follow-up over the next seven years.

In March 2006, the patient noted redness on the nasal side of the right bulbar conjunctiva. A mass was palpable at the superior nasal edge. The best-corrected visual acuity was 1.2 in both eyes. The anterior segments and fundi of both eyes were normal. In June 2006, a salmon-pink lesion was noted in the lower fornix of the right eye (Fig. 4) and another mass was palpable inferior to the eye globe in the left orbit. Magnetic resonance imaging showed a mass on the nasal side of the right orbit (Fig. 4). Excisional biopsy through the right eye conjunctiva showed T-cell/histiocyte-rich diffuse large B-cell lymphoma (Fig. 3). In the context of the patient exhibiting recurrence of systemic lymphadenopathy, treatment with retuximab was initiated.

METHODS

Histopathology and immunohistochemistry

The sections of the paraffin-embedded tissues stored from 1990 for Patient #1 and from 1999 for Patient #2 were reevaluated by hematoxylin-eosin stain and standard immunohistochemical staining. Paraffin sections were cut and deparaffinized with xylene and graded ethanol series. The sections were stained with hematoxylin-eosin and were prepared for immunohistochemistry. Sections were incubated with 3% hydrogen peroxide for 5 min to inactivate endogenous peroxidase, and blocked with 10% normal goat serum for 10 min. The sections were then incubated with primary antibodies overnight at 4°C, washed with 0.05% Tween 20-containing phosphate buffered saline three times, incubated with the second antibody at room temperature for 30- 60 min, and washed. The color was developed with diaminobenzidine and the nuclei were counterstained with hematoxylin.

Immunoglobulin heavy chain gene rearrangement

Immunoglobulin heavy chain gene rearrangement was detected by polymerase chain reaction (PCR).[11,12] Unstained formaldehyde-fixed, paraffin sections placed on slide glasses were deparaffinized with xylene and graded ethanol series and samples for DNA isolation were cut out from at least two different areas of the deparaffinized section. The amplifica-

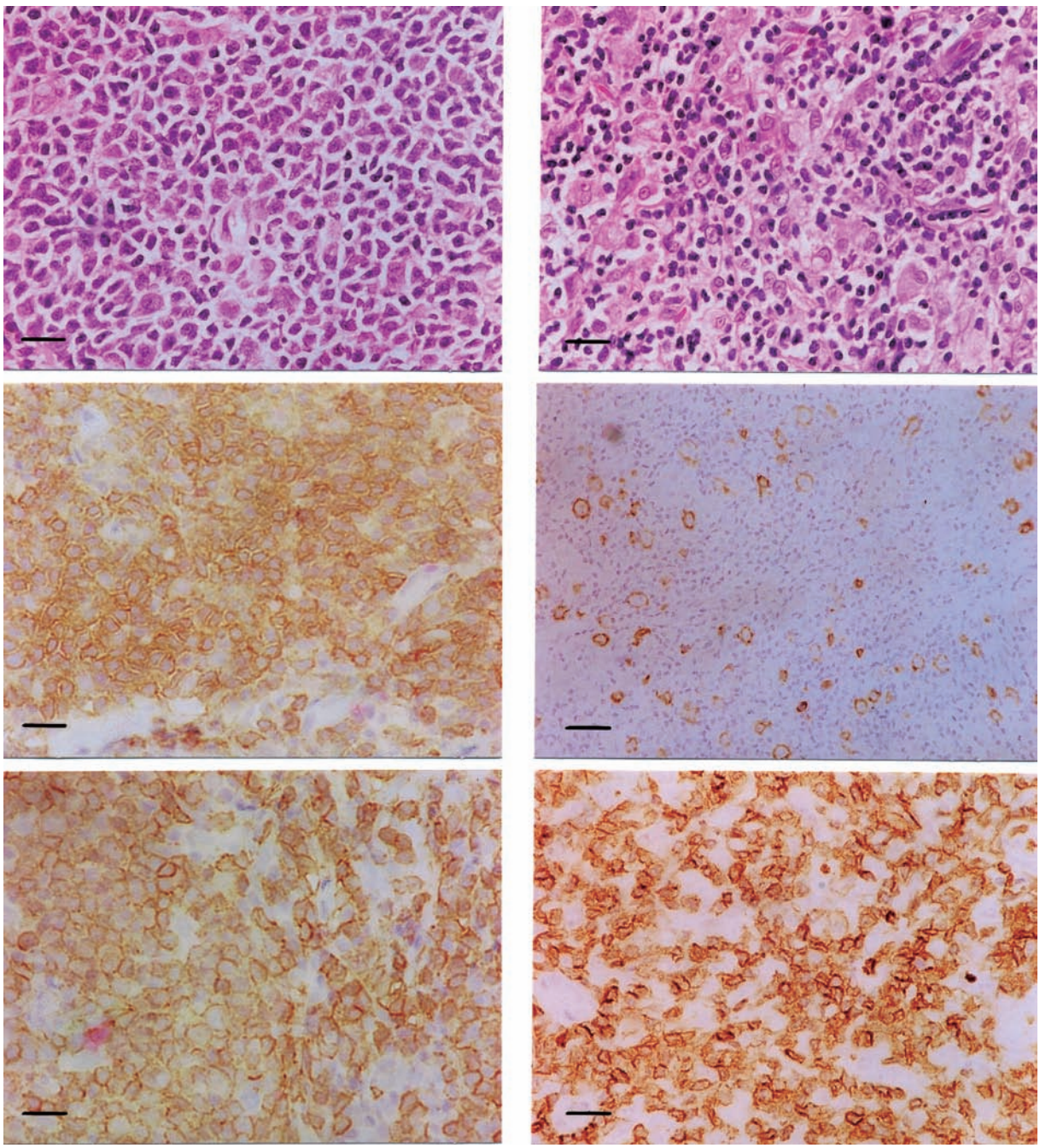


Fig. 3. Patient #2. Follicular lymphoma on inguinal lymph node biopsy in 1999 (*left column*) and T-cell/ histiocyte-rich diffuse large B- cell lymphoma on right orbital biopsy in 2006 (*right column*). Centrocyte-like cells (*left top*) are positive to CD10 (*left middle*) and CD79a (*left bottom*). Large transformed cells in a small number (*right top*) are positive to CD20 (*right middle*) while small lymphocytes (*right top*) are CD3- positive T-cells (*right bottom*). *Bar* = 20 μm.

tion of immunoglobulin heavy chain genes was performed by semi-nested PCR, using primers directed to the framework 2 region (FR2A : 5'-TGGRTCCGMCAGSCYYCNGG-3' for both the first and the second PCR) and to the joining region (LJH : 5'-TGAGGAGACGGTGACC-3' for the first PCR and VLJH : GTGACCAGGGTNCCTTGGCCCCAG-3' for the second PCR). At least two DNA samples from each paraffin section were separately subjected to PCR with TAKARA Ex Taq (Takara Bio Inc., Otsu, Japan). The amplified products from each patient were electrophoresed in paral-

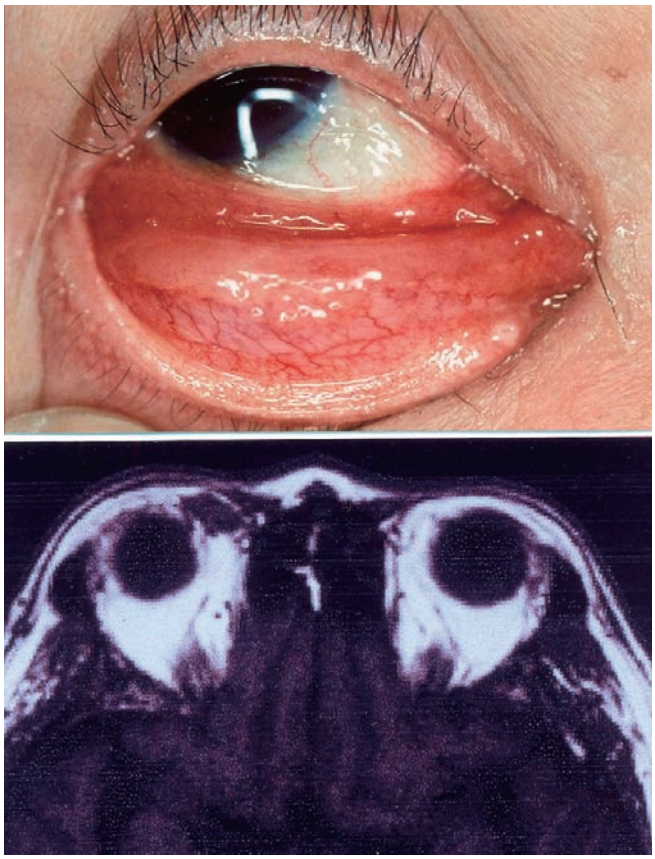


Fig. 4. Patient #2 in 2006. Salmon-pink lesion in the lower fornix of the right eye (*top*) and a magnetic resonance image showing the mass on the nasal side of the right orbit (*bottom*).

lel in 3% agarose gel. The determination of "clonal" was made only when a single or dominant discrete band was consistently reproduced from different specimens.[11]

For the sequencing of the clonal bands, the PCR products were purified with ExoSAP-IT (USB, Cleveland, OH) and used as a template for direct sequencing with the ABI 310 Genetic Analyzer (Perkin-Elmer, Foster, CA) using the BigDye Terminator Cycle Sequencing Kit (Perkin-Elmer) and either of the two primers (FR2A and VLJH) to sequence in both directions. At least two PCR products from different samples derived from the same tissue were sequenced in both directions. Nucleotide changes were defined as those which repeatedly occurred between the two different tissues.

RESULTS

Histopathology and immunohistochemistry

For Patient #1, the supraclavicular lymph node biopsy specimen obtained in 1990 showed follicular growth patterns only with a small number of large transformed cells with round or oval or indented nuclei, peripheral nucleoli, and a narrow rim of cytoplasms, appearing like centroblasts (Fig. 1). The lymphoma cells were positive for CD20 and bcl-2, weakly positive for CD10, but negative for CD3 or CD5. In contrast, the orbital biopsy specimen obtained in 2006 had small to medium-sized lymphoid cells in vaguely nodular growth patterns (Fig. 1). These lymphoid cells had slightly irregular nuclei, inconspicuous nucleoli, and relatively abundant, pale cytoplasms, which appeared like centrocytes. Immunohistochemically, the lymphoid cells were positive for CD20 and bcl-2, but negative for CD3, CD5, or CD10. The number of Ki-67-positive cells was small.

For Patient #2, the inguinal lymph node biopsy specimen obtained in 1999 showed follicular growth patterns with small to medium-sized cells with angulated, twisted or cleaved nuclei, inconspicuous nucleoli, and scant pale cytoplasms, appearing like centrocytes (Fig. 3). The small number of cells was large transformed centroblast-like cells. The lymphoma cells were positive for CD10, CD20, CD79a, and bcl-2, but negative for CD3 or CD5. In contrast, the orbital biopsy specimen obtained in 2006 showed diffuse growth pattern which consisted of a large number of small lymphocytes and histiocyte-like cells, admixed with a small number of large transformed cells which had oval to round nuclei, prominent nucleoli, and scant cytoplasms, and which had centroblast-like appearances (Fig. 3). The large transformed cells were positive for CD20 and Ki-67, but negative for CD3, CD5, or CD10 whereas the small lymphocytes were positive for CD3.

Immunoglobulin heavy chain gene rearrangement

In analyzing the biopsy specimens for Patient #1 in 1990 and 2006 using PCR of the immunoglobulin heavy chain gene, neither a single nor a dominant discrete band was amplified. The 1990 lymph node specimen showed no amplification at all while the 2006 orbital specimen showed a ladder of bands. In contrast, the 1999 and 2006 specimens for Patient #2 each showed a single discrete band in the same size around 250 base pairs (Fig. 5), supporting the same clonality of neoplastic cells between the original lymph node lesion and the recurrent orbital lesion. The direct sequencing in both directions of the amplified products from the 1999 and 2006 specimens in this patient revealed the same sequence except for 5 nucleotide changes noted in comparing these specimens (Fig. 6).

DISCUSSION

Follicular lymphoma has follicular growth patterns and usually consists of two types of cells, centrocytes and centroblasts, which are found in follicle centers, namely, germinal centers. These lymphoma cells are usually positive for CD10 and bcl-2, and also positive for B-cell associated antigens

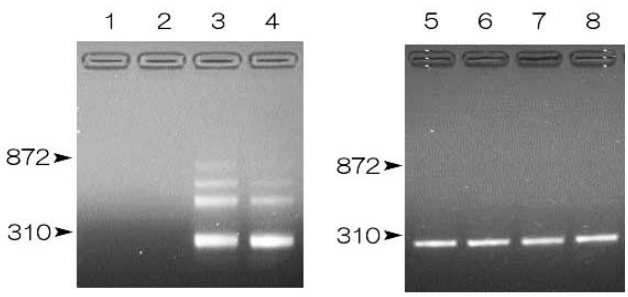
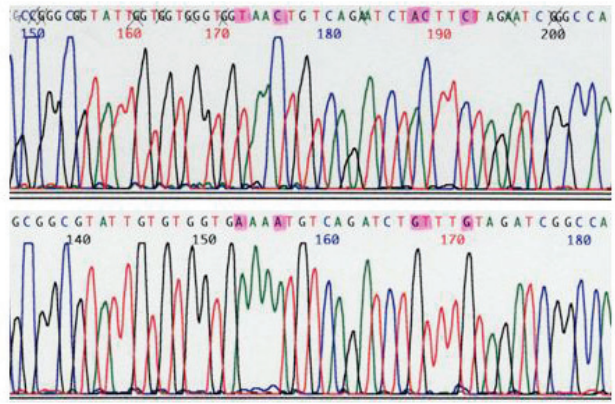


Fig. 5. Polymerase chain reaction amplification of an immunoglobulin heavy chain gene rearrangement. The 1990 lymph node specimen (*lanes 1 and 2*) shows no amplification at all while the 2006 orbital specimen (*lanes 3 and 4*) shows a ladder of bands in Patient #1. In contrast, the 1999 lymph node specimen (*lanes 5 and 6*) and 2006 orbital specimen (*lanes 7 and 8*) in Patient #2 show a single dominant discrete band of the same size. Size markers (phage X174 DNA Hae III digest, base pairs) are given on the left for each figure plate.



Lymph node lesion
GCGGCGTATTGTGTGGTG**T**AA**C**TGTCAGATCT**AC**TT**C**TAGATCGGCCA
Orbital lesion
GCGGCGTATTGTGTGGTG**A**AA**A**TGTCAGATCT**GT**TT**G**TAGATCGGCCA

Fig. 6. Direct sequencing of polymerase chain reaction products with the same DNA size derived from the 1999 lymph node specimen and the 2006 orbital specimen in Patient #2. The sequences are in forward direction with the primer directed to the framework 2 region (FR2A) and are the same except for five nucleotide changes (*in bold*) between the lymph node lesion (*top*) and the orbital lesion (*bottom*).

such as CD20 and CD79a. The lymphoid cells both in Patient #1 in 1990 and in Patient #2 in 1999 showed follicular growth patterns. The lymphoma cells in Patient #1 were weakly positive for CD10 while the lymphoma cells in Patient #2 were positive for CD10. CD10 is a good marker for follicular lymphoma but not necessarily positive in all cases. Postulated cells of origin for follicular lymphoma are germinal center B-cells.

Patient #1 showed the recurrence in 2006 as a MALT lymphoma of the orbit. In general, the neoplastic cells in MALT lymphoma infiltrate around reactive B-cell follicles, external to a preserved follicle mantle, in a marginal zone distribution. The typical marginal zone B-cells are medium-sized cells with slightly irregular nuclei, inconspicuous nucleoli, and relatively abundant, pale cytoplasms that resemble centrocytes. The lesion occasionally contains lymphoma cells with plasmacytic differentiation and also a small number of large transformed cells resembling centroblasts or immunoblasts. Postulated cells of origin of MALT lymphoma are post-germinal-center, marginal zone B-cells, and therefore, are at different levels in B-cell differentiation lineage compared to those in follicular lymphoma. The MALT lymphoma in Patient #1 could be independent of the preceding follicular lymphoma in regard to the clonality of neoplastic cells.

The amplification of the immunoglobulin heavy chain gene by PCR gave rise to no band from genomic DNA of the lymph node specimen of Patient #1 obtained in 1990. The poor quality of the DNA due to strong fixation of the tissue used in older years would account for the failure to produce any PCR results in the lymph node specimen of this patient. Another explanation would be the fact that follicular lymphomas are renowned for false negative PCR results, due to the large number of somatic mutations in the variable region of the immunoglobulin heavy chain gene. Such situations would prevent the primers from binding in the PCR. In contrast, a ladder of bands was amplified from genomic DNA of the orbital specimen obtained in 2006, which did not present evidence of clonality. Such a ladder of bands could be generated from the presence of normal lymphocytes admixed with lymphoma cells. It should be therefore noted that PCR remains unreliable in revealing the clonality of lymphoma.[11,12] Thus, for Patient #1, PCR amplification of the immunoglobulin heavy chain gene rearrangement did not support the same clonality of the1990 lymph node and the 2006 orbital specimen.

Over the years, there have been a few case reports describing the simultaneous development of follicular lymphoma and MALT lymphoma in different tissues of the same patient.[13,14] In addition, one case report described a woman with a 12-year history of Sjögren syndrome who developed MALT lymphoma in the parotid gland and then presented generalized lymphadenopathy and hepatosplenomegaly with the diagnosis of follicular lymphoma two years later.[7] In reverse sequence, with an unusually long interval of 16 years, Patient #1, in this study, showed follicular lymphoma and orbital MALT lymphoma. In the previous studies, PCR amplification of the immunoglobulin heavy chain gene rearrangement supported the same clonality[7] or different clonalities[13,14] of lymphoma cells between MALT lymphoma and follicular lymphoma.

Patient #2 showed the recurrence in 2006 of T-cell/histiocyte-rich diffuse large B-cell lymphoma in the orbit. According to the World Heath Organization Classification of

Tumors published in 2001, T-cell/histiocyte-rich diffuse large B-cell lymphoma is a morphologic variant of diffuse large B-cell lymphoma and is characterized by the predominance of non-neoplastic T-cells admixed with a small number of large neoplastic B-cells.[15,16] The postulated origin of cells in diffuse large B-cell lymphoma is either germinal center or post-germinal-center B-cells. The neoplastic B-cells in both follicular lymphoma and diffuse large B-cell lymphoma share germinal center B-cells as postulated cells of origin. On the contrary, immunophenotypic and genetic analyses of 30 cases of T-cell/histiocyte-rich diffuse large B-cell lymphoma showed a lack of connection to follicular lymphoma.[17] In Patient #2, T-cell/histiocyte-rich diffuse large B-cell lymphoma is thus either independent of follicular lymphoma or arising from follicular lymphoma in regards to the clonality of neoplastic cells.

PCR amplification of the immunoglobulin heavy chain gene rearrangement showed a single discrete band with the same size from the genomic DNA of both the 1999 lymph node specimen and the 2006 orbital specimen of Patient #2. In addition, the bands from the two different tissues had the same DNA sequence except for five separate nucleotide changes. Basically, the same DNA sequence with minor nucleotide changes would support the same clonality shared by the preceding lymph node lesion and the later orbital lesion. Follicular lymphoma is known to transform to diffuse large B-cell lymphoma.[5] In recent studies, genomic changes have been revealed to occur during the transformation from follicular lymphoma to diffuse large B-cell lymphoma.[18,19] In Patient #2, additional nucleotide changes could have developed in the immunoglobulin heavy chain gene of lymphoma cells of the same clonal origin in the 16-year process of the transformation from follicular lymphoma to diffuse large B-cell lymphoma.[5]

The goal of this study is to document the fact that orbital lymphomas occur as a recurrence of systemic lymphomas which have initially developed 16 years previously. In the present series, the two cases shared follicular lymphoma as an initial histopathological type of lymphoma. This fact might occur by chance only, or it might be attributed to the tendency of follicular lymphomas to take an indolent course. Follicular lymphoma was observed without treatment in Patient #1 while follicular lymphoma showed a relapse after combination chemotherapy and radiation in Patient #2. The second lymph node biopsy from Patient #2's 1999 relapse still showed the same histopathological type of follicular lymphoma as the first lymph node biopsy from the initial presentation in 1990.

The patients described here and the previously documented cases[5] also show that malignant lymphoma can recur as a different histopathological type compared to the initial type noted. Furthermore, immunohistochemical and PCR-assisted genetic analyses in past studies support the fact that the clonalities of the neoplastic cells are not necessarily the same between the original lesion and the recurrent lesion.[5] In this study, the clonality appears to differ between the original lymph node lesion and the recurrent orbital lesion in Patient #1, while the original lymph node and recurrent orbital lesions shared the same clonality in Patient #2.

We previously documented a patient who developed systemic diffuse large B-cell lymphoma many years after bilateral orbital pseudotumor.[20] In contrast, this study reports two patients who developed orbital lymphomas many years after systemic lymphoma. In view of the fact that orbital lymphoid lesions, in general, include both malignant lymphoma and reactive lymphoid hyperplasia such as orbital pseudotumor, these lesions must be carefully evaluated. Orbital lymphoid lesions can develop as the long-interval recurrence of systemic lymphoma or can present as the original lesion for the future development of systemic lymphoma.

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