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Review Article

Pathology of Follicular Lymphoma

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Follicular lymphoma (FL) is a heterogeneous disease, and there are many different subgroups, such as in terms of age of onset, involved organ (especially extranodal sites such as gastrointestinal tract) and genetic abnormality. Grade 3B is currently regarded as a distinct entity by molecular genetic analyses, but the independence of Grade 3A remains unclear. Variations of clinical course are known in FL. Some cases are very indolent, but others are not. The latter cases show histological transformation to diffuse large B-cell lymphoma (DLBCL) (high-grade transformation) and an aggressive course. Histological transformation to DLBCL is reported to occur in about 30-40% of patients, at a rate of about 3% each year. However, it reaches a plateau at about 16 years, so the stratification of patients in whom transformation would or would not occur is very important for the therapeutic strategy. From genome-wide analysis by next-generation sequencing, *EZH2*, *CREBBP* and *MLL2*, which are histone-modifying genes, have been shown to be frequently mutated in FL and to have an important role in lymphomagenesis. *IGH-BCL2* translocation and *CREBBP* mutations are early events, whereas *MLL2* and *TNFSFR14* mutations represent late events during disease evolution. In the 2008 WHO classification, three new variants: (1) pediatric follicular lymphoma, (2) primary intestinal follicular lymphoma and (3) *in situ* follicular lymphoma, are included. Pathologists and clinicians should consider these new developments when deciding on the diagnostic and therapeutic strategy. 〔*J Clin Exp Hematop 54(1): 3-9, 2014*〕

Keywords: follicular lymphoma, heterogeneity, molecular genetics, WHO classification, extranodal follicular lymphoma

INTRODUCTION

Follicular lymphoma (FL) is the second most common low-grade B-cell lymphoma after mucosa-associated lymphoid tissue (MALT) lymphoma. It occurs at a rate of about 20% in Western countries. In Japan, the rate was about 6% during 1996-2000. However, it has increased since 2000. In our surgical files, the frequency of FL was about 15% in 2009 and about 17% in 2011, so it is approaching that of Western countries. The cause of this increase is still unknown, but it generally develops in middle-aged and elderly people (median age 60 years old from our patient files). It also occurs at a younger age, such as under 20 years old, on rare occasions. The most commonly involved site is the lymph nodes, but sometimes extranodal sites, such as gastrointestinal sites, especially the duodenum, as well as the skin, thyroid gland, salivary gland, breast and testis, are involved. Against this background, three new variants : (1) pediatric follicular lymphoma, (2) primary intestinal follicular lymphoma and (3) *in situ* follicular lymphoma, are included in the 2008 WHO classification.[1]

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GRADING OF FOLLICULAR LYMPHOMA

FL has been the subject of various classifications according to the proportion of large centroblastic cells. In the Rappaport classification, there were five subgroups: I: Lymphocytic type, well differentiated; II: Lymphocytic type, poorly differentiated (lymphoblastic); III: Mixed type (lymphocytic and reticulum cell); IV: Reticulum type; and V: Hodgkin's type.[2] In the Working Formulation classification, three subgroups were included: (1) follicular, predominantly small cleaved cells; (2) follicular mixed, small cleaved and large cells (FM); and (3) follicular, predominantly large cells.[3] In addition, the R.E.A.L. classification, which was established in 1994, has three subgroups: Grade I: predominantly small cleaved; Grade II: mixed small and large cells; and Grade III: predominantly large cells, follicular center lymphoma, diffuse, small cells.[4] The third edition of the WHO classification inherited this approach and proposed a classification according to the number of centroblastic cells, namely, Grade 1 (0-5/hpf), Grade 2 (6-15/hpf) and Grade 3 (> 15/hpf). Grade 3 was also divided into Grade 3a (centrocytes present) and Grade 3b (solid sheets of centroblasts).[5] At the time of revision for the fourth edition of the WHO classifica-

tion, grading of FL was discussed in various ways, for example, counting of centroblasts and associations with clinical prognosis, but the grading was similar to that in the third classification. The modifications were as follows: the description of Grades 1-2 (low grade; 0-15 centroblasts/hpf) was accepted, and the notation of Grades 3a and 3b was changed to Grades 3A and 3B.[1]

It is important to distinguish between Grade 3A and Grade 3B because there are apparent differences of clinical prognosis and molecular genetics between them. Bosga-Bouwer *et al*. examined 29 Grade 3B patients by fluorescence *in situ* hybridization (FISH) and immunohistochemical study, and divided them into three subgroups: (1) 3q27/BCL6 break (+) and t(14;18) translocation (−), (2) 3q27/BCL6 break (−) and t(14;18) translocation (−) and (3) 3q27/BCL6 break (−) and t(14;18) (+). They described that the t(14;18) (+) group and the 3q27/BCL6 break (+) group were mutually exclusive, and that the 3q27/BCL6 break (+) group was associated with DLBCL.[6] Katzenberger *et al*. reported that patients of Grade 3B with a DLBCL component frequently exhibited 3q27/BCL6 break.[7] Furthermore, Karube *et al*. described that MUM-1 was frequently expressed in Grade 3B samples.[8] As such, it was suggested that Grade 3A FL is on the same spectrum as Grade 1-2 FL, and Grade 3B FL behaves the same as *de novo* DLBCL. However, Hans *et al*. and Chau *et al*. reported that there were no significant differences in overall survival and event-free survival between Grade 3A and 3B subgroups.[9,10] As such, Grade 3B will be a distinct entity by molecular genetic analyses, but the entity of Grade 3A is still unclear and requires further study.

CLINICAL FEATURES

Variations of clinical course are known in FL. Some cases are very indolent, but others are not. The latter cases show histological transformation to diffuse large B-cell lymphoma (high-grade transformation) and exhibit an aggressive course.

FL patents are usually at an advanced stage, with only 26-33% of patients being in stage I/II.[11] Histological transformation to DLBCL is reported to occur in about 30-40% of patients, at a rate of about 3% each year.[12] Although the median overall survival of all patients with FL is 6-10 years, patients die within a year if high-grade transformation occurs. On the other hand, about 20% of cases are reported to show spontaneous regression without treatment.[13] As mentioned above, FL is a heterogeneous disease from a clinical perspective.

HISTOLOGICAL CHARACTERISTICS AND IMMUNOPHENOTYPE

The normal counterpart of FL is germinal center-derived B cells (GCB cells). Tumor cells are composed of small to medium-sized cleaved cells (centrocytes) and large non-cleaved cells (centroblasts), and form follicle structures. Neoplastic follicles have vague borders and scant or absent mantle zones. Normal follicles have tingible body macrophages but neoplastic ones of Grade 1/2 do not, and show a monotonous appearance (Fig. 1A, 1B). If the number of large cells is more than 15/HPF, the diagnosis is Grade 3. Grade 3A has a mixture of centrocytes, but Grade 3B has no centrocytes and shows sheet-like proliferation of centroblasts. In immunohistochemistry, tumor cells are positive for B-cell markers such as CD20 and CD79a, and negative for T-cell markers such as CD3 and CD5. Reflecting the GCB derivation, tumor cells are positive for CD10 and BCL6. Although BCL2 protein is down-regulated in normal germinal centers

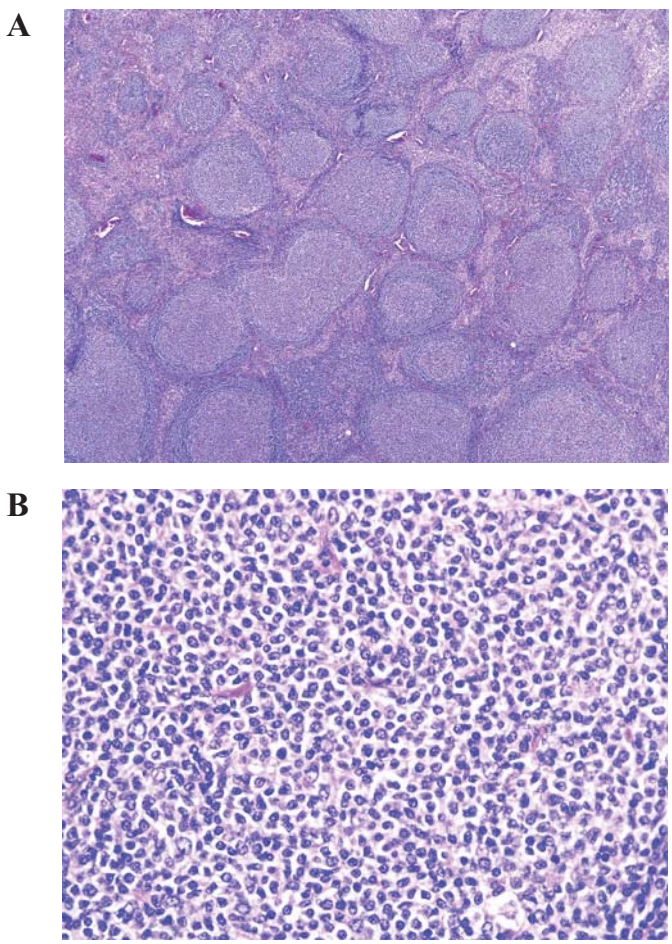

Fig. 1. Histological appearance of nodal follicular lymphoma. (***1A***) Low-power field of follicular lymphoma, Grade 1 (H&E stain, ×40). Neoplastic follicles have vague borders and scant or absent mantle zones. (***1B***) High-power field of follicular lymphoma, Grade 1 (H&E stain, ×200). Tumor cells are composed of small to medium-sized cleaved cells (centrocytes) and large non-cleaved cells (centroblasts).

and causes apoptosis of non-selected B cells, tumor cells always express BCL2 protein by t(14;18)/IGH-BCL2. This is thought to be one of the causes of lymphomagenesis. t(14;18)/IGH-BCL2 can be detected by long-distance polymerase chain reaction or FISH.[14] It was reported that t(14;18)/IGH-BCL2 can be detected in most cases, but not in 10-20% of Grade 1/2 cases ; the rate of negativity is 10% in our series. Half of the Grade 3 cases are reported to be negative for this translocation.[1]

Some histological variations are reported, such as "follicular lymphoma with marginal zone differentiation," which shows differentiation to marginal zone or monocytoid B cells, "floral variant," "hyaline vascular variant," which has hyaline collagenous fiber proliferation (Fig. 2), "inverted variant" (Fig. 3), and "signet ring cell variant."

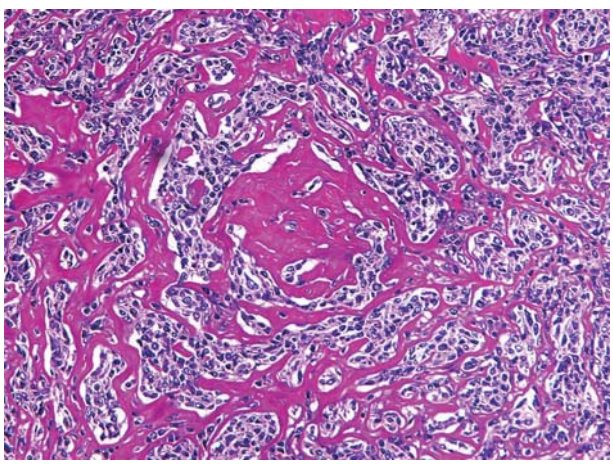

Fig. 2. Hyaline vascular variant of follicular lymphoma. Hyalinized vessels are present at the tumor follicle. H&E stain, × 200.

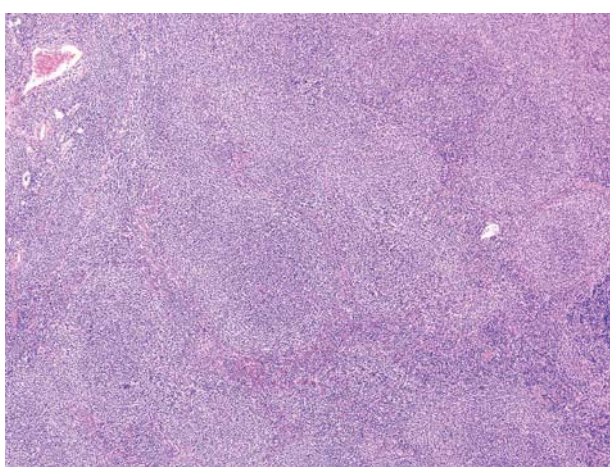

Fig. 3. Inverted variant of follicular lymphoma. Central zone of the tumor follicles is darker than the peripheral zone of follicles. H&E stain, × 40.

DIFFERENTIAL DIAGNOSIS

Low-grade B-cell lymphomas that are composed of nodular structures should be differentiated. They are marginal zone B-cell lymphoma, mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma. Tumor cells of marginal zone B-cell lymphoma proliferate in marginal zone areas and sometimes have follicular colonization. They often show differentiation to monocytoid B cells or plasma cells. Immunostaining of CD10 is useful to recognize regressed germinal centers. In follicular lymphoma cases, tumor follicles show stronger CD10 immunostaining than reactive lymphoid follicles.[15] MCL is usually differentiated by cyclin D1 positivity on immunostaining. From a histological perspective, MCL shows monotonous medium-sized cell proliferation, pink macrophages and atrophic germinal centers. Chronic lymphocytic leukemia/small lymphocytic lymphoma forms nodular structures composed of small to medium-sized tumor cells, and within them, proliferation centers composed of prolymphocytes and paraimmunoblasts are seen. Tumor cells are positive for CD5 and CD23 by immunostaining.

MOLECULAR GENETICS

Several genetic abnormalities have been reported by array comparative genomic hybridization (CGH), FISH and DNA microarray analyses.[16-20] Representative abnormalities in addition to IGH-BCL2 translocation were as follows: break points in chromosome 1, deletions in the long arm of chromosome 6 (6q), trisomy 7 (7), trisomy 12 (12), presence of a derivative of chromosome 18 (der (18)) and duplication of X (X).[21] Loss of chromosomal material at 6q25-27 was a strong independent predictor of inferior survival.[22] Deletions in 1p36.22-p36.33 and 6q21-q24.3 were also highly associated with transformation and inferior overall survival in patients with FL using array CGH.[23] Schwaenen *et al*. reported a large number of recurring genomic aberrations in FL as analyzed by array CGH, of which deletions in 9p21 (*CDKN2A/B*), 6q25 and 6q26 were associated with inferior survival.[24] In addition, O'Shea *et al*. reported that acquired uniparental disomy of 1p36 is a prognostic factor and acquired uniparental disomy of chromosome 16 is associated with histological transformation.[25]

In recent years, genome-wide analysis of several types of cancer including malignant lymphoma by next-generation sequencing (NGS) has become available and important somatic mutations in germinal center-derived B-cell lymphomas, such as FL, have been discovered. In particular, it has been found that genetic abnormalities accumulate at the cluster of histone-modifying genes. Morin *et al*. reported that *EZH2* (Y641), which encodes a histone methyltransferase responsible for tri-methylating H3K27, was mutated in GCB DLBCL

(21.7%) and FL (7.2%), whereas this was not found in activated B-cell-like DLBCL.[26] In addition, *MLL2*, which also encodes a histone methyltransferase, was frequently mutated in DLBCL (32%) and FL (89%).[27] Morin *et al*. and Pasqualucci *et al*. described that inactivating mutations of *CREBBP* and *EP300*, which belong to the KAT3 family of histone/protein lysine acetyltransferases, occur in 39% of DLBCL and 41% of FL (Pasqualucci *et al*.), and in 11.4% of DLBCL and 13.4% of FL (Morin *et al*.).[27,28] There were differences in frequency between these two reports, but the findings are reliable, in that these were recurrent mutations, and suggest that histone-modifying gene mutations play important roles in germinal center-derived lymphomagenesis.

Green *et al*. separated the FL tumor cells by CD20 expression intensity and examined and compared primary FL samples and relapsed FL samples by NGS analysis. They found out that IGH-BCL2 translocation and CREBBP mutations are early events, whereas *MLL2* and *TNFSFR14* mutations represent late events during disease evolution.[29] Recently, in this way, it was suggested that a minor population of tumor cells is associated with tumor relapse.

HISTOLOGICAL TRANSFORMATION

Histological transformation is reported to occur at a frequency of about 40% of all FL patients, but varies among previous reports.[30-33] It causes abrupt lactate dehydrogenase elevation and emergence of extranodal lesions, among others, and then becomes a major factor behind therapy resistance and poor prognosis. The frequency of transformation is reported to be 3% each year.[12] However, it reaches a plateau at about 16 years, so the stratification of patients in whom transformation would or would not occur is very important for the therapeutic strategy. Both abnormality of neoplastic cells and that of the microenvironment are thought to be important for the transformation. For neoplastic cells, loss of tumor suppressor genes such as *p53* and *CDKN2A* and amplification of *MYC* oncogene and its target genes are known.[34-37] For the microenvironment, loss of follicular dendritic cell (FDC) meshworks and/or increase of CD4-positive T cells in the intrafollicular area have been reported.[38,39] Kiaii *et al*. reported that, by gene expression analysis of CD4-positive and CD8-positive T cells that interact with FL cells, expression of 3 genes : *PMCH*, *NAMPT* and *ETV1*, in inter- and intrafollicular T cells is an important risk factor for the transformation.[40]

PEDIATRIC FOLLICULAR LYMPHOMA

FL in the pediatric population is rare, occurring as only 1-2% of all malignant lymphomas and only one case in our experience. FL in the pediatric population has a distinct biological behavior and clinical picture ; it was documented as a variant in the WHO classification of 2008. Common sites are cervical lymph node and tonsil, but lesions of testis, gastrointestinal tract, salivary duct, kidney or skin have been reported on rare occasions.[1] Lorsbach *et al*. analyzed 23 cases of pediatric FL and found that most cases were at stage I/II (16/23). There were high frequencies of histological Grade 3 (9/23) and negativity of BCL2 (11/23). Such cases respond well to therapy, although they have high-grade morphology, histologically.[41]

"*IN SITU*" FOLLICULAR LYMPHOMA

"*In situ*" follicular lymphoma/intrafollicular neoplasia is thought to involve BCL2-positive tumor follicles in reactive lymphoid follicular hyperplasia. Cong *et al*. performed a microdissection study for BCL2-positive follicles and BCL2-negative follicles ; a monoclonal band was detected only in BCL2-positive follicles.[42] From a long-term follow-up of *in situ* follicular lymphoma by Jegalian *et al*., only one of 21 patients progressed to overt FL.[43] In the peripheral blood of healthy individuals, IGH-BCL2 translocation was detected in about half of Western people and about 30% of Japanese people in a polymerase chain reaction study.[44-45] It is thought that these B cells with IGH-BCL2 translocation will acquire additional abnormal genetic change and may expand in the reactive follicles.

PRIMARY INTESTINAL FOLLICULAR LYMPHOMA

Gastrointestinal follicular lymphoma, especially duodenal follicular lymphoma, frequently occurs as extranodal FL. We have reported that duodenal follicular lymphoma is frequently found at the second part of the duodenum and exhibits indolent clinical behavior.[46] With the growing popularity of this concept among gastroenterologists and pathologists, the frequency of diagnosis in duodenal follicular lymphoma is increasing. Recently, it has also been shown that lymphoma cells spread to the small intestine (jejunum and ileum), as determined by double-balloon endoscopy and capsule endoscopy.[47]

We conducted multicenter retrospective analysis from 18 consecutive institutions (gastrointestinal follicular lymphoma study group). One hundred and twenty-five of 191 patients were at stage I or II1 by Lugano's classification, and were thought to have the gastrointestinal tract as the primary site (in 70 patients, the whole of the gastrointestinal tract was studied). The most common involved site was the second part of the duodenum (54/70 ;77%), followed by the jejunum and the ileum. In addition, 85% of the cases involved a wide spread to the small intestine ; in other words, only 15% of duodenal follicular lymphomas were localized to the duodenum (Fig. 4A, 4B). Furthermore, the involvement of the

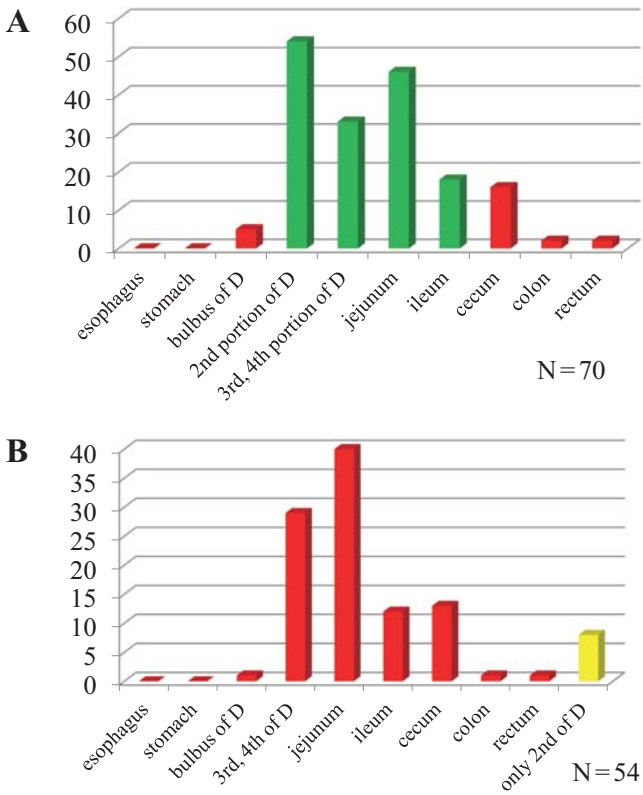

Fig. 4. Tumor distribution of gastrointestinal follicular lymphoma (examined by double-balloon endoscopy and/or capsule endoscopy). (***4A***) Tumor cells are widely distributed at the small intestine (duodenum, jejunum and ileum). (***4B***) Tumor distribution of patients with positivity at the second duodenal part. Eighty-five percent of duodenal follicular lymphomas spread to the jejunum and/or ileum.

second portion of the duodenum was an independent prognostic factor for progression-free survival.[48]

The typical macroscopic appearance is small white nodules with multiple lesions (Fig. 5A). Histologically, small to medium-sized lymphoid cells with tumor follicles are present at the proper mucosal area. In addition, tumor cells frequently involve mucosal villi (Fig. 5B, 5C). More than 95% of gastrointestinal follicular lymphomas are at Grade 1-2 (low grade). Immunohistologically, tumor cells are positive for CD10 and BCL2, the same as for nodal follicular lymphoma. In our previous study of a series of 30 patients with duodenal follicular lymphoma, 27 samples (90%) presented the same CD21 (FDC) expression pattern, which lacked FDC meshworks and was found at the periphery of tumor follicles.[49] This pattern (duodenal pattern) corresponded to follicular colonization in MALT lymphoma. In contrast, follicular lymphoma of the stomach and colon had FDC meshworks like nodal follicular lymphoma.[50] Translocation of IGH-BCL2 was highly detected (about 87%) by FISH analysis in duodenal follicular lymphoma.[49]

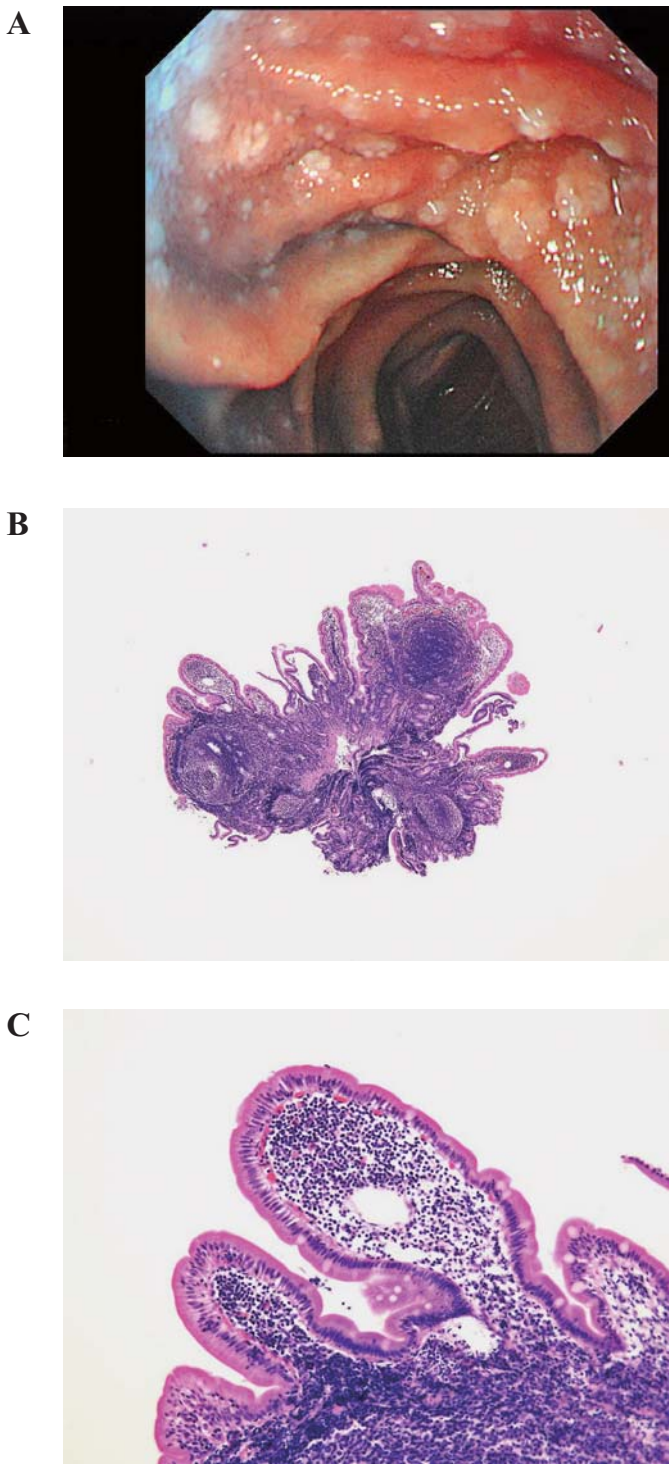

Fig. 5. Macroscopic and microscopic appearance of duodenal follicular lymphoma. (***5A***) Macroscopic features of duodenal follicular lymphoma. Typical macroscopic appearance is small white nodules with multiple lesions. (***5B***) Histologically, small to medium-sized lymphoid cells with tumor follicles are present at the proper mucosal area. H&E stain. ×4. (***5C***) Tumor cells involve duodenal mucosal villi. H&E stain, ×40.

With regard to the molecular pathogenesis, we reported that immunoglobulin heavy-chain usage (VH usage) deviated to VH4 and VH5, and there were many of the same usages of VH genes, such as VH4-34, VH3-23 and VH3-73. These results suggested that duodenal follicular lymphoma is similar to MALT lymphoma.[49] Furthermore, duodenal follicular lymphoma lacks activation-induced cytidine deaminase, despite having somatic hypermutation and ongoing mutation. From our comprehensive gene expression study, duodenal follicular lymphoma is very similar to MALT lymphoma and has distinct characteristics within the group of follicular lymphomas (manuscript under submission).

CONCLUSION

Follicular lymphoma is a very heterogeneous disease, and there are many different subgroups, such as in terms of age of onset, involved organ (especially extranodal sites such as gastrointestinal tract) and genetic abnormality. As such, it is desirable that principles for its diagnosis and therapy are established.

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