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Original Articles

Frequent Expression of CD10 and Bcl-6 in High-Grade Primary Extranodal Lymphoma with Diffuse Large B-cell Lymphoma Morphology

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The distinction of *de novo* diffuse large B-cell lymphomas (DLBCL) from transformed MALT lymphomas is difficult in the absence of MALT-component. This study aims to study the phenotypic expression profiles of extranodal lymphomas, focusing on the characteristics of high-grade tumors. We categorized 52 extranodal B-cell lymphomas into Grade 1 (low-grade MALT lymphoma), Grade 2 (DLBCL with MALT component), and Grade 3 (DLBCL without MALT component) tumors based on histomorphology. There were 26 (50%) Grade 1, 9 (17%) Grade 2, 15 (29%) Grade 3 tumors. We could not assess the grade of two tumors (4%) due to limiting tumor tissues. The expression of CD10, Bcl-2, Bcl-6, and p53 was also investigated by immunohistochemistry. CD10 expression was present in one Grade 1 and six Grade 3 tumors. Bcl-6 expression was more common in high-grade tumors ($p=0.001$), while Bcl-2 expression was associated with lower-grade tumors ($p=0.001$). CD10 expression was more useful as a marker in distinguishing Grade 2 from Grade 3 tumors than Bcl-6 expression. p53 was more frequently expressed in high-grade tumors; the higher frequency of p53 expression in Grade 2 tumors may suggest a potential role in the transformation of Grade 1 to Grade 2 tumors.
Key words MALT lymphoma, DLBCL, CD10, Bcl-2, Bcl-6

INTRODUCTION

Extranodal lymphomas, commonly of the gastrointestinal tract, comprise of approximately 25% to 40% of non-Hodgkin's lymphomas (NHLs)[1,2]. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the most common form, comprising up to 30% of extranodal lymphomas and accounting for 7% to 8% of total B-cell lymphomas[1,3]. Low-grade MALT lymphoma, which has been extensively described, exhibits prominent lymphoepithelial lesions and/or follicular colonization by small- to medium-sized centrocyte-like cells[1,2,4]. These tumors can also often exhibit moderate cytological atypia of neoplastic lymphocytes and infiltrating plasma cells containing Dutcher's bodies[1,2,4,5].

Although low-grade MALT lymphoma is regarded as clinically indolent, high-grade transformation is common[6-8]. Previous studies have reported that approximately 20% to 35% of gastric lymphomas are actually *de novo* diffuse large B-cell lymphomas (DLBCL)[9-11]. The distinction of *de novo* DLBCL from transformed MALT lymphoma, however, is not possible in the vast majority of cases, due to the absence of MALT component[5,12]. Recent WHO classification stated that instead of using the term 'high-grade MALT lymphoma', all large B-cell lymphomas should be diagnosed as DLBCL, with only a reference to the presence or absence of MALT components[1]. As extranodal *de novo* DLBCL and transformed MALT lymphomas do not differ in either prognosis or overall survival, clinical studies support this decision. Individually, the outcome of these diseases is poorer than that observed for low-grade MALT lymphoma, but significantly better than nodal DLBCL[9-11,13].

Based on studies of the phenotypic expres-

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sion and genotypic characteristics of the immunoglobulin gene in tumors, the normal counterpart of the neoplastic MALT lymphoma cells is postulated to be a post-germinal center marginal zone B-cell[1,4,14,15]. MALT lymphoma tumor cells lack specific markers, and are usually identified by exclusion[1,2]. The expression of CD10 and Bcl-6 appear to be reliable markers of germinal center derivation[16–19]; CD10 expression is also strongly associated with the t (14; 18) translocation[20,21]. Hence, CD10 expression may help to distinguish the subset of *de novo* DLBCL derived from post-germinal center transformed MALT lymphomas. Rare cases of low-grade MALT lymphomas have been reported to express CD10, which may further complicate difficulties distinguishing these lymphomas[22–26]. The expression of Bcl-6, however, was only reported in transformed MALT lymphomas, but not low-grade MALT lymphomas[24,27–29]. Hans *et al.*[30] demonstrated that MUM1/IRF4 expression may be useful in differentiating Bcl-6$^+$ germinal center cells (MUM1$^-$) from Bcl-6$^+$ cells that have not yet entered germinal centers (MUM1$^+$).

Bcl-2 protein is frequently expressed in low-grade MALT lymphomas, but is absent from high-grade tumors[31–35]. As Bcl-2 can block apoptosis to extend the survival of resting B-cells[36], these cells can acquire secondary genetic changes over time that can result in progression to DLBCL[35]. The partial inactivation of *p53* through mutation or allelic loss may be associated with the development of low-grade MALT lymphoma, while complete inactivation may contribute to transformation into a high-grade tumor[6].

Even though extranodal *de novo* DLBCL and transformed MALT lymphomas do not differ in prognosis and overall survival, these diseases may represent distinct biological entities undergoing different lymphomagenic processes. This study aims to assess the efficacy of a panel of immunophenotype markers as a mechanism to differentiate low-grade MALT lymphomas, transformed MALT lymphomas, and extranodal *de novo* DLBCL.

MATERIALS AND METHODS

Case Selection

Fifty-two biopsies from 48 patients previously diagnosed with extranodal B-cell lymphomas over a period of 6 years, from 1994 to 1999, were retrieved from the archives of University of Malaya Medical Centre for the study. Clinical information was extracted from records volunteered by patients and attending clinicians. The tumors examined were taken from extranodal sites, with these sites being the only or most extensively affected locations. Patients with a previous history of nodal B-NHL were excluded from this study. Differential diagnoses excluded small-cell extranodal lymphomas, such as mantle cell lymphoma, small lymphocytic lymphoma, and follicular lymphoma by the absence of markers associated with those diseases according to previously established criteria: CD5 and cyclinD1 expression for mantle cell lymphoma, CD5 and CD23 expression for small lymphocytic lymphoma, and CD10 and Bcl-6 expression for follicular lymphoma[1,2,4,12].

Histological Grading

Tumors were sub-classified as low-grade MALT lymphoma (Grade 1), DLBCL with evidence of transformed MALT lymphoma (Grade 2), and DLBCL without any evidence of MALT component/*de novo* DLBCL (Grade 3), according to the histological system proposed by Isaacson[4]. The categorization of low-grade MALT lymphoma was based on histomorphological features[1]: 1) dense infiltration of small- to medium-sized centrocytic-like cells with irregular nuclei and relatively abundant pale cytoplasm, 2) the accumulation of infiltrating centrocyte-like cells in the epithelium leading to destruction, forming a lymphoepithelial lesion, 3) the presence of reactive follicles that may be infiltrated by centrocyte-like cells, leading to follicular colonization, 4) presence of transformed centroblast- or immunoblast-like cells, and 5) extensive plasma cell differentiation. A tumor was considered to be high-grade DLBCL when the tumor cells were large, centroblast- or immunoblast-like, and present in compact or sheet-like proliferative foci.

Immunophenotyping and analysis

Immunoperoxidase staining of 4-μm-thick paraffin sections utilized the Avidin-Biotin Complex (ABC) system (DakoCytomation, Glostrup,

Denmark), StrepABC system (DakoCytomation), and the indirect two-step detection system, EnVision+™ (DakoCytomation). Antigen retrieval was performed accordingly by the microwave heat-inducing method, pressure-cooking, or trypsin digestion. The tissues were stained with a panel of antibodies against lymphoid markers. Antibodies against CD20 (L26), CD3, CD21 (clone 1F8), Bcl-2 (clone 124), Bcl-6 (clone PG-B6p), and p53 (clone DO-7) were obtained from DakoCytomation. Antibodies specific for CD5 (NCL-5), CD10 (NCL-CD10-270), CD23 (NCL-Cd23-1B12), CD35 (NCL-CD35), and cyclinD1 (NCL-CYCLIN D1-GM) were purchased from Novocastra (Newcastle upon Tyne, UK). An anti-IRF-4 antibody (clone sc-11450) was acquired from Santa Cruz Biotechnology (CA, USA). Antibody staining was visualized using the liquid DAB$^+$ substrate-chromogen system (DakoCytomation). Tissues were lightly counter-stained with hematoxylin.

Estimation of the numbers of tumor cells expressing p53 protein classified the tumors into the following categories: $<$10% (negative), 10–25% (low), 25–50% (moderate), $\geq$50% (high).

Follicular colonization was assessed with the aid of immunostaining for CD21, CD23, CD35, CD10, Bcl-2, and Bcl-6. CD21, CD23, and CD35 identify follicles through staining of follicular dendritic cell networks. B cells present within reactive germinal centers are typically CD10$^+$/Bcl-6$^+$/Bcl-2$^-$. During follicular colonization, CD10$^+$/Bcl-6$^+$ germinal center cells were replaced by infiltrating bcl-2$^+$ tumor cells (CD10$^-$/Bcl-6$^-$/Bcl-2$^+$).

Statistical Analysis

Statistical analysis was performed by using the Pearson χ^2 test (SPSS for Windows) with a 95% confidence interval.

RESULTS

Case Data

This study included 48 patients, four of which had two biopsies each, giving a total of 52 biopsies. These 48 patients, 26 males (54%) and 22 females (46%), ranged in age from 20 to 87 years, with a mean and median of 58 and 62 years, respectively. The age of one (2%) patient was not available from the clinical records. Of the 52 biopsies, 42 (81%) were from the gastrointestinal tract. Thirty-two of these were from the stomach, three were from the small intestine, two each were from the duodenum, colon, and caecum, and one from the rectum. The remaining 10 (20%) biopsies were from the orbit (4), thyroid (2), subconjunctival mass (1), tongue (1), lung (1), and cheek muscle (1).

Histological Grade

Of the 52 biopsies, 26 (50%) were categorized as Grade 1 (Fig. 1a), 9 (17%) were determined to be Grade 2 (Fig. 1b), and 15 (29%) were classified as Grade 3 tumors (Fig. 1c). The grade of two (4%) gastric biopsies could not be determined due to limited amounts of tumor tissue. The tumors of the gastrointestinal tract were divided into 18 (43%) Grade 1, 9 (21%) Grade 2, and 13 (31%) Grade 3 tumors. We could not observe a correlation between histological grade and site of presentation within the gastrointestinal tract ($p=0.204$). All biopsies from other sites were determined to be Grade 1 (8/10, 80%) tumors, with the exception of the tongue and thyroid samples that were both Grade 3 (2/10, 20%) tumors. Lymphoepithelial lesions were observed in 13/26 (50%) Grade 1 tumors and 3/9 (33%) of Grade 2 tumors. Of the Grade 1 tumors, lymphoepithelial lesions were found in 11/18 (61%) of gastrointestinal tract samples, in contrast to 2/8 (25%) from other extranodal sites.

Immunophenotype Pattern

While all of the tumors expressed CD20, we could not observe CD5, CD23 and cyclinD1 expression in any samples. CD10 and Bcl-6 were expressed in seven and 14 tumors, respectively. Of these tumors, CD10 and Bcl-6 were co-expressed in three tumors. CD10 and Bcl-6 expressions according to histological grade are summarized in Table 1. Of the 11 CD10$^-$/Bcl-6$^+$ tumors, five (45%) expressed IRF-4 (one Grade 2 and four Grade 3 tumors). All CD10$^+$ tumors were classified as Grade 3, with the exception of one Grade 1 tumor, indicating a significant ($p=0.005$) association of CD10 expression with higher-grade classification. In contrast, CD10 expression was not associated with an origin within the gastrointestinal tract ($p=0.165$). The CD10$^+$

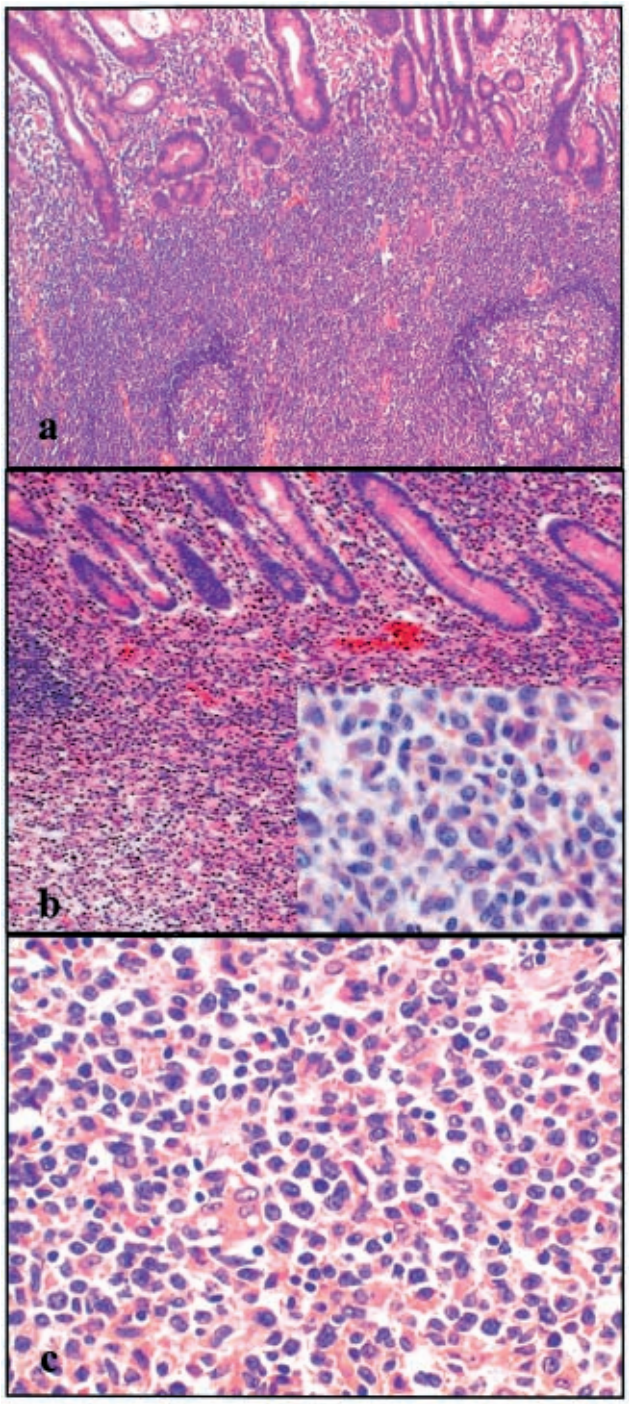

Fig. 1. Histological features of tumors of different histological grades. a) A low-grade MALT lymphoma (Grade 1 tumor) demonstrated the infiltration of centrocyte-like cells and the presence of reactive lymphoid follicles (H&E, ×55). b) A diffuse large B-cell lymphoma contained a MALT component (H&E, ×55) (insert, H&E, ×325) (Grade 2 tumor). c) A diffuse large B-cell lymphoma lacking a MALT component (Grade 3 tumor) exhibited the diffuse infiltration of large cells (H&E, ×325).

Grade 1 tumor contained prominent lymphoepithelial lesions (Fig. 2a). Within this sample, while CD10 was expressed in almost all tumor cells (Fig. 2b), Bcl-6 was expressed sporadically in scattered blasts (Fig. 2c), in contrast to the intense staining seen throughout Grade 3 tumors (Fig. 2d).

Bcl-6 protein was expressed in 2/26 (8%) Grade 1 (including the biopsy co-expressing CD10), 4/8 (50%) Grade 2, and 8/13 (61%) Grade 3 tumors. The reactivity of Bcl-6 staining in 4 biopsies could not be determined due to technical problems. The expression of Bcl-6 protein was significantly associated with higher grade tumors (Grade 2 and Grade 3) ($p=0.001$), but not with CD10 expression ($p=0.480$). Bcl-6 was not associated with tumor origin within the gastrointestinal tract ($p=0.454$).

Bcl-2 protein was expressed by the tumor cells in 30/52 (58%) biopsies, including 21/26 (81%) Grade 1, 4/9 (44%) Grade 2, 3/15 (20%) Grade 3 tumors, and 2/2 (100%) tumors that could not be histologically assessed. While significantly associated with Grade 1 tumors ($p=0.001$), Bcl-2 expression exhibited an inverse association with CD10 expression ($p=0.012$); only one Grade 3 tumor co-expressed CD10 and bcl-2. Bcl-2 expression in tumors of the gastrointestinal tract did not differ from those in other extranodal sites ($p=0.102$).

The follicular dendritic cell network was visualized by staining with anti-CD21 (Fig. 3a), anti-CD23, and anti-CD35 (Fig. 3b) antibodies in 28, 18, and 31 of the total biopsies, respectively. Follicular colonization (Fig. 3c & 3d) was observed in 19/26 (73%) Grade 1 and 2/9 (22%) Grade 2 tumors. Reactive lymphoid follicles were detected in 22/26 (85%) Grade 1, 4/9 (44%) Grade 2, and 2/15 (13%) Grade 3 tumors. Reactive lymphoid follicles correlated significantly with Grade 1 tumors ($p<0.001$).

The majority of samples expressed p53 protein in less than 10% of the total tumor cells (35/51, 67%). One biopsy was not reactive for p53 immunostaining. Of the Grade 1 tumors, only one each exhibited moderate and high levels of p53 protein expression. Only five (10%) biopsies expressed p53 protein in $\geq$ 50% of the tumor cells. p53 expression was not associated with Bcl-2 expression ($p=0.461$).

Table 1 CD10 and Bcl-6 expression in tumors of different histological grades

Histological Grade	$CD10^{+\dagger}$ / $Bcl\text{-}6^{+\ddagger}$	$CD10^{+}$/ $Bcl\text{-}6^{-}$	$CD10^{-}$/ $Bcl\text{-}6^{+}$	$CD10^{-}$/ $Bcl\text{-}6^{-*}$
1	1	0	1	24
2	0	0	4^	4
3	2	4	6^	1
NA	0	0	0	1
Total	3	4	11	30

† CD10 expression was associated with Grade 3 tumors ($p=0.005$)

‡ Bcl-6 expression was associated with high-grade tumors ($p=0.001$)

* Excluded four biopsies that were not reactive for Bcl-6 staining

NA Not histologically assessable

^ One Grade 2 and four Grade 3 tumors expressed MUM1/IRF4 protein

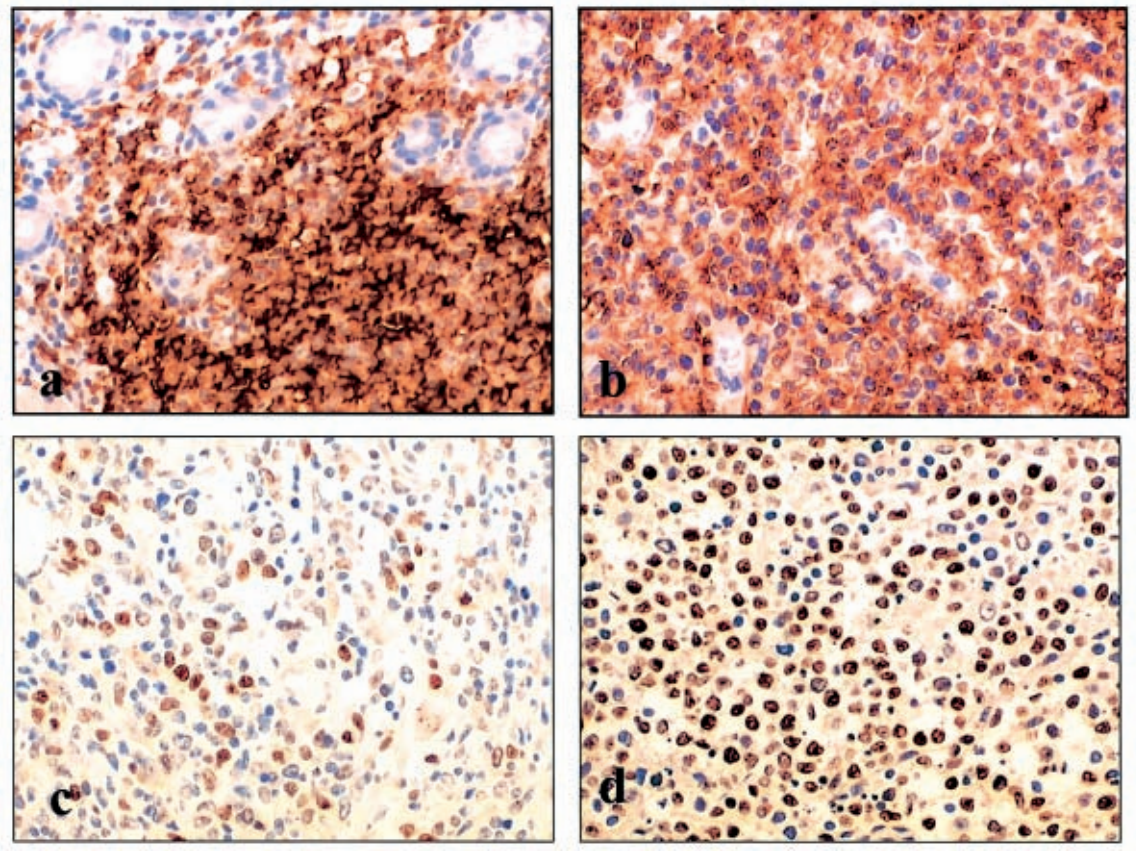

Fig. 2. Immunostaining of a $CD10^{+}/Bcl\text{-}6^{+}$ low-grade MALT lymphoma (a—c) and a Grade 3 tumor (d). a) $CD20^{+}$ B-cells were observed infiltrating the epithelium, forming the characteristic lymphoepithelial lesion (CD20 immunostain, ×280). b) Almost all tumor cells expressed CD10 (CD10 immunostain, ×280). c) Bcl-6 was expressed sporadically by scattered blasts (Bcl-6 immunostain, ×280). d) A Grade 3 tumor sample exhibited diffusely intense staining for Bcl-6 (Bcl-6 immunostain, ×280).

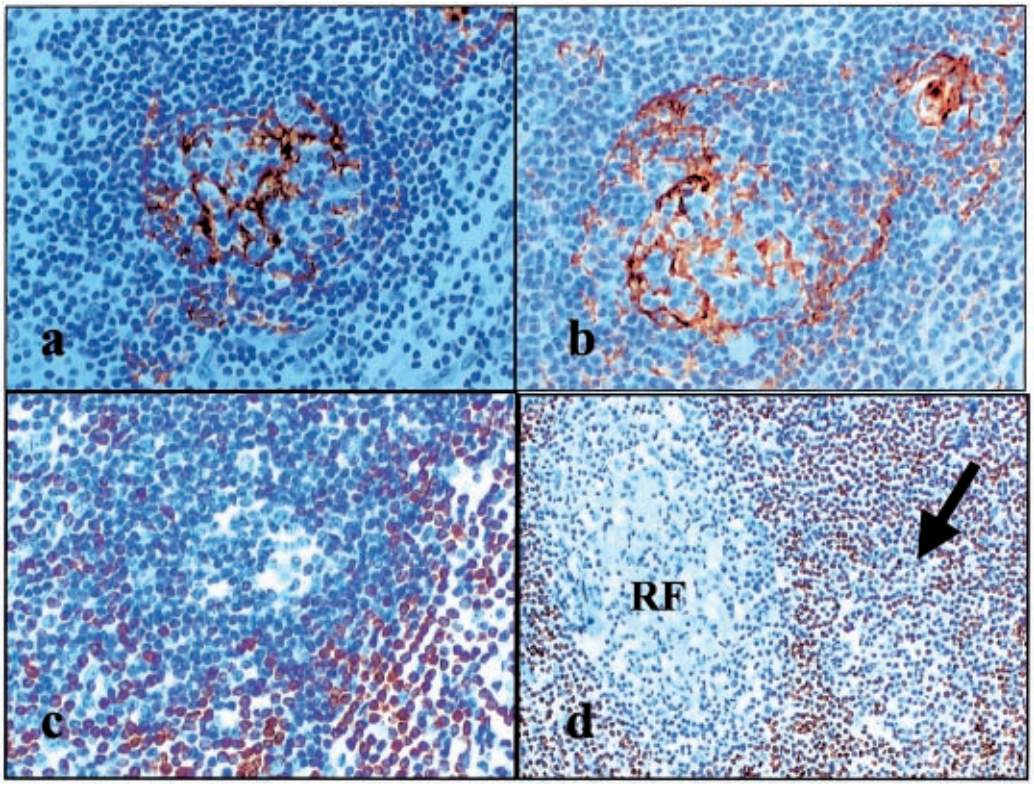

Fig. 3. The follicular dendritic cell network and follicular colonization as visualized by immunstaining. The follicular dendritic cell network in a Grade 1 tumor (Case 2) was demonstrated by a) CD21 (CD21 immunostaining, ×260) and b) CD35 (CD35 immunostaining, ×260) staining. c) Bcl-2 staining of the same follicles in (a) & (b) demonstrated the infiltration of tumor cells into the follicles (Bcl-2 immunostaining, ×260). d) An additional Grade 1 tumor exhibited Bcl-2$^+$ centrocyte-like cells infiltrating the reactive follicles, indicated by the black arrow, while the adjacent reactive follicle (RF) is devoid of Bcl-2$^+$ cells (Bcl-2 immunostaining, ×135).

Table 2 Bcl-2 and p53 expression according to the histological grades

Histological Grades	Bcl-2*	p53**			
		<10% (Negative)	10%–25% (Low)	25%–50% (Moderate)	>50% (High)
Grade 1	21/26	20/26	4/26	1/26	1/26
Grade 2	4/9	5/8	0/8	1/8	2/8
Grade 3	3/15	10/15	2/15	1/15	2/15
NA	2/2	0/2	2/2	0/2	0/2

*Bcl-2 expression was significantly associated with Grade 1 tumors ($p=0.001$)

**One biopsy was not reactive for p53 immunostaining

DISCUSSION

MALT lymphomas exhibit a spectrum of morphological characteristics, ranging from low-grade tumors that resemble benign *Helicobacter pylori*-associated gastritis to high-grade tumors resembling nodal DLBCL. Chronic gastritis and low-grade MALT lymphoma share many features, including the presence of centrocytic-like cells, reactive follicles, and small lymphocytes infiltrating the lamina propria and epithelium[37]. Thus, distinguishing these conditions remains a

challenge in some cases[38]. While prominent lymphoepithelial lesions serve as a conclusive criterion separating neoplastic from reactive proliferation, this feature was only found in 48% and 38% of Grade 1 and Grade 2 tumors in the current series, respectively. This result is in agreement with previous reports, in which lymphoepithelial lesions were only observed in one third of the cases[5,12]. As lymphoepithelial lesions may be missed due to limiting quantities of tissues evaluated, Zukerberg *et al.*[5] suggested that sufficient sampling of the biopsies is essential to detect these lesions. Lymphoepithelial lesions were rarely observed in non-gastric Grade 1 tumors. The presence of centrocytic-like cells and germinal center surface markers were the most consistent features observed in Grade 1 tumors. Positive staining for markers characteristic of germinal centers, found in 85% of examined tumors, was also significantly associated with low-grade MALT lymphoma.

Transformation of low-grade MALT lymphomas into higher-grade tumors is signified by the emergence of increasing numbers of blasts and the formation of sheet-like blast clusters[4,7,8,39,40]. It is almost impossible to differentiate Grade 2 from Grade 3 tumors in the absence of a MALT component. The potential for MALT component to be missed in small biopsies[41,42] further complicates the differentiation of Grade 2 and Grade 3 tumors. Chan[2] noted that gastric DLBCL, regardless of the presence or absence of a MALT component, exhibited an increased frequency of *c-myc* gene rearrangement (50%) and reduced frequency of Bcl-2 expression from the levels observed in the equivalent nodal DLBCL. Grade 2 and Grade 3 tumors do not differ clinically in their prognosis and overall survival[9–11,13]. Cogliatti *et al.*[10] reported that the 5-year survival for extranodal DLBCL was significantly worse than that seen for Grade 1 tumors.

Even though the histological features do not support the separation of Grade 2 and Grade 3 tumors, the immunophenotypic profiles do exhibit differences in expression profiles. Grade 2 tumors were more similar to Grade 1 tumors, with a notable absence of CD10 expression. Grade 1 and Grade 2 tumors displayed a general immunophenotypic profile of $CD20^+/CD5^-/CyclinD1^-/CD10^-/CD23^-/CD21^-$. While none of the Grade 2 tumors expressed CD10, 47% of the Grade 3 tumors expressed this marker. Statistical analysis demonstrated that the increased incidence of CD10 expression in Grade 3 tumors was significant. This result suggests the possibility that a substantial proportion of these Grade 3 tumors were not derived from low-grade MALT lymphomas. These $CD10^+$ Grade 3 tumors were more likely *de novo* extranodal DLBCL derived from germinal centers, as reported by previous studies[9–11]. We cannot confirm, however, that the $CD10^-$ Grade 3 tumors were derived from MALT lymphomas, as nodal DLBCL transformed from follicular lymphomas also tend to lose CD10 expression[43]. Moreover, CD10 expression is only reported in 20% to 30% of nodal DLBCL[43,44].

Although CD10 is reportedly a reliable marker for germinal center derivation[16–19], it can be expressed in rare cases of B-cell marginal zone lymphomas[22–26]. In this study, we observed one $CD10^+$ Grade 1 tumor with prominent lymphoepithelial lesions, small- to medium-sized centrocytic-like cells, and few blasts. Our observation agrees with at least four additional reports that rare Grade 1 tumors can express CD10[22,23,25,26]. In addition, Kwon *et al.*[24] reported the expression of CD10 in 3/20 of the examined Grade 2 (high-grade MALT lymphoma) tumors.

Bcl-6 protein expression has been reported in both germinal center-derived cells[16,17,19] and non-germinal center cells[19]. Tumor cells of true germinal center derivation exhibit an intense diffuse expression pattern, in comparison to the sporadic expression seen in non-germinal center cells[19,24]. The sporadic Bcl-6 expression pattern observed in the $CD10^+$ Grade 1 tumor was similar to the pattern described by Ree *et al.*[19] and Kwon *et al.*[24]. Blasts expressing Bcl-6 in this Grade 1 tumor may be residual reactive follicle center cells that have been trapped within the tumor[16,24]. Takeshita *et al.*[45] suggested that de-differentiation or re-entry of tumor cells into germinal centers during follicular colonization may reactivate Bcl-6 protein expression, resulting in rare $Bcl\text{-}6^+$ marginal zone B-cells. The remaining two cases of Grade 3 tumors co-expressing CD10 and Bcl-6, in which intense expression of Bcl-6 was observed in nearly all tumor cells, are likely to represent tumors of germinal center derivation. In contrast, 45% of $CD10^-/Bcl\text{-}6^+$ tumors expressed the MUM1/IRF4 protein, indicating derivation from activated B-cells[30]. Chang *et al.*[46] suggested that these

tumor cells may represent a third group of DLBCL derived from activated germinal center B-cells. This hypothesis may not be true for a subset of Grade 2 tumors, as MUM1/IRF4 expression has also been shown in 42% of extranodal marginal zone lymphomas[47]. The expression of Bcl-6 by the subjects in this report agreed with previous studies; high expression levels were only observed in high-grade DLBCL, regardless of MALT component[27,28,48]. Bcl-6 protein expression may be associated with the high-grade transformation of low-grade MALT lymphomas[27].

We observed a decreasing frequency of Bcl-2 expression in high-grade tumors, concurring with previous studies that demonstrate the loss of Bcl-2 protein upon progression of low-grade MALT lymphomas into high-grade tumors[31–35]. The frequent expression of Bcl-2 in low-grade MALT lymphomas suggest that this protein plays an important role in lymphomagenesis, potentially acting through its ability to block apoptosis[31–33,35]. Escape from apoptosis increases the incidence of other genetic abnormalities that may ultimately lead to neoplastic transformation. The expression of Bcl-2 protein does not define neoplastic low-grade MALT lymphoma, as this molecule is frequently expressed by hyperplastic marginal zone cells[49]. Although the role of Bcl-2 in the lymphomagenesis of MALT lymphomas requires further investigation, the increased expression in low-grade tumors may simply reflect the intact regulation of Bcl-2 in cells derived from such marginal zone B-cells. In this study, the frequency of Bcl-2 expression was significantly lower in high-grade DLBCL than in low-grade MALT lymphomas. It is also plausible that, as tumors progress acquire high-grade character, additional genetic abnormalities may abrogate the need for Bcl-2 in tumor survival[33,35,50].

Higher levels of p53 expression ($\geq$50%) were observed in Grade 2 tumors (25%) in comparison to the levels seen in Grade 1 (4%) and Grade 3 (13%) tumors. Higher p53 protein expression in Grade 2 tumors suggests that the mutation of the *p53* gene may play a role in the transformation of low-grade to high-grade MALT lymphomas. This possibility is supported by molecular evidence that genetic inactivation of *p53* is important for the transformation of low-grade MALT lymphomas into high-grade tumor[6]. According to Stefanaki *et al.*[51], mutation of *p53* gene was detected in 33% of Grade 2 tumors, in comparison to 19% of Grade 1 tumors. All Grade 2 tumors with positive p53 immunostaining contained missense mutations of the *p53* gene. Therefore, it is speculated that mutation of *p53* gene may be required for the transformation of the low-grade MALT lymphomas into high-grade tumor. The expression of p53 protein in Grade 3 tumors was in agreement with reports of nodal DLBCL (17% to 40%)[13,52].

In conclusion, the diagnosis of low-grade MALT lymphoma requires a combination of histomorphological and immunophenotypic characteristics. Although rare cases of low-grade MALT lymphoma have been reported to express an aberrant immunophenotype, including markers such as CD5 and CD10, this lymphoma typically expresses an immunophenotype of $CD20^+/CD3^-/CD5^-/cyclinD1^-/CD10^-/CD23^-$. CD10 expression is useful to differentiate between Grade 3 and Grade 2 tumors, while bcl-6 expression is correlated with high-grade tumors. Bcl-2 protein is frequently expressed in low-grade tumors, but is usually lost in high-grade tumors. The pattern of p53 protein expression suggests that mutation of the *p53* gene may function in the transformation of low-grade MALT lymphomas into high-grade tumor.

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