

## ***Helicobacter pylori* and Gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma: Updated Review of Clinical Outcomes and the Molecular Pathogenesis**

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In most *H. pylori*-positive patients, gastric low-grade mucosa-associated lymphoid tissue (MALT) lymphomas regress both endoscopically and histopathologically after *H. pylori* eradication, but no factors that can be predictive of the response to the eradication have been definitively identified, and there is little information on how to determine the optimal observation period before additional treatment can be started. Here, clinical studies dealing with the diagnosis and treatment of gastric MALT lymphomas and *H. pylori* published during the last 5 years were systematically reviewed, and studies identifying the molecular approaches involved in the pathogenesis were summarized. Most of the clinical studies indicate a favorable effect of *H. pylori* eradication on the clinical outcome of gastric MALT lymphomas. Some studies suggest the necessity of additional treatment in nonresponders to *H. pylori* eradication, while others suggest the adoption of a watch-and-wait strategy. The molecular characteristics of MALT lymphomas could play an important role in prognostic prediction and the selection of further therapeutic intervention after the eradication. This updated review of gastric MALT lymphomas illustrates the potential efficacy of *H. pylori* eradication in tumor remission, but further molecular characterization is necessary to establish the most suitable therapeutic strategy for patients who do not respond to eradication. (**Gut and Liver 2009;3:81-87**)

**Key Words:** *Helicobacter pylori*; Eradication; *API2-MALT1* fusion; BCL10; CD20

### INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a gram-negative, micro-aerobic rod that lives in the gastric mucous layer, on the surface epithelial cells.<sup>1</sup> *H. pylori* infection causes gastric mucosal inflammation, which could not only lead to chronic gastritis and peptic ulcer disease, but also to gastric adenocarcinoma or low-grade mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>1</sup> *H. pylori* eradication has become a widely accepted initial treatment strategy for stage I gastric marginal zone B cell lymphoma of MALT. Although in 60-80% of these cases, *H. pylori*-positive low-grade B-cell gastric MALT lymphoma regress both endoscopically and histopathologically after *H. pylori* eradication,<sup>2,3</sup> both the factors that might be predictive of the response to the eradication therapy, as well as the optimal duration of observation needed prior to the potential start of additional second-line treatment in the non-responsive cases remain controversial.

### LITERATURE REVIEW FOR GASTRIC MALT LYMPHOMA

A literature search was performed in PubMed using the keywords [gastric MALT lymphoma] and [*H. pylori*] for the publications during the last 5 years (2004-2008). After accumulating the list of included studies, publications not related to either gastric MALT lymphoma or *H. pylori* were excluded. In addition, the recent developments in the molecular mechanisms involved in the pathogenesis of gastric MALT lymphomas were reviewed.

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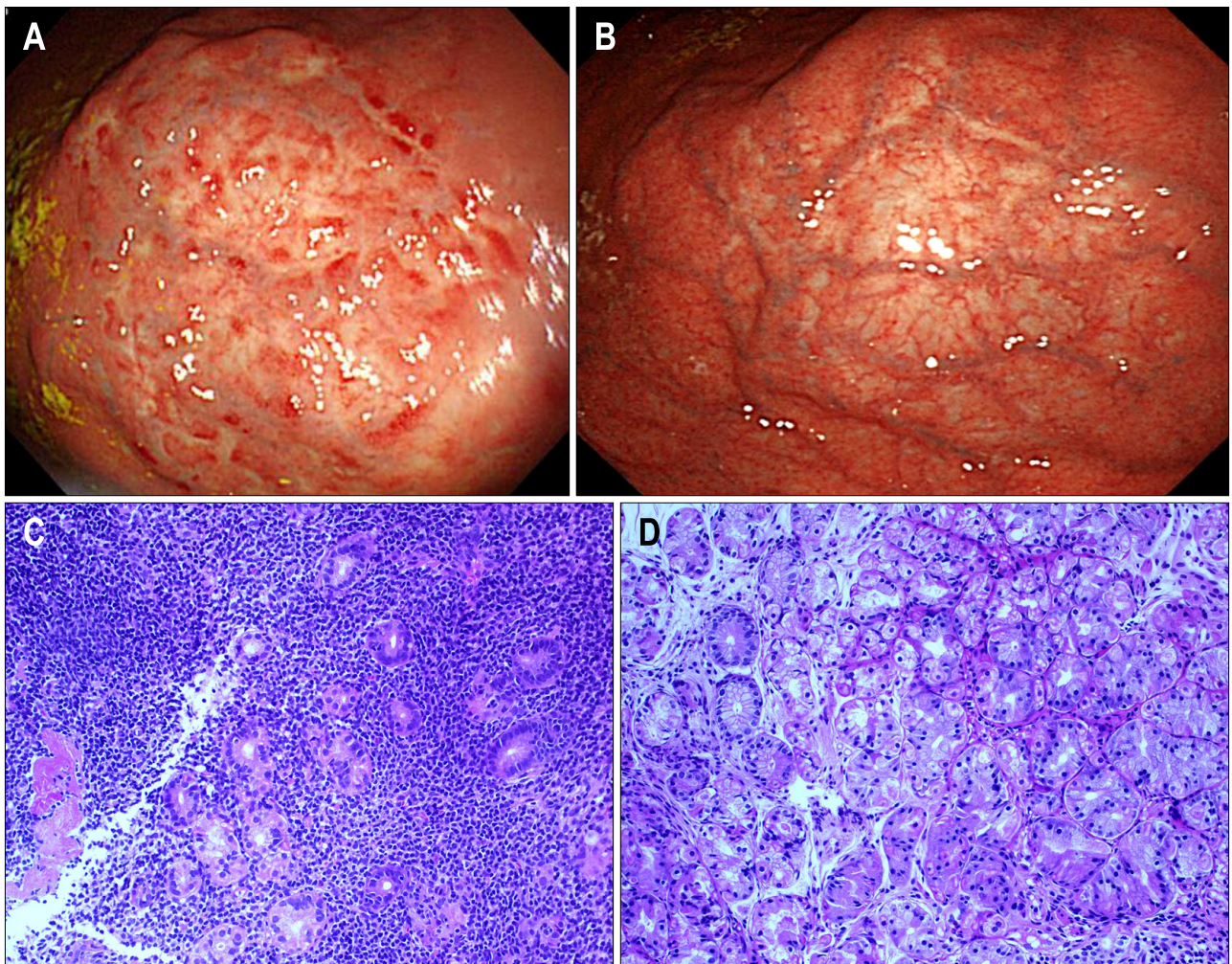
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The initial search yielded 21 manuscripts. Among these, 6 articles (1 review article, 3 articles dealing with non-gastric MALT lymphomas, and 2 articles not dealing with *H. pylori*) were excluded, while the remaining 15 were carefully reviewed. Among the 15 articles reviewed, 4 articles<sup>4-7</sup> dealt with the diagnosis and the remaining 11 dealt with the treatment of gastric MALT lymphomas. Among the 11 articles dealing with the treatment, 9 articles<sup>8-16</sup> reported on *H. pylori* eradication, 1 article<sup>17</sup> reported reconsideration of surgical treatment after a median follow-up of 11.5 years after gastrectomy, and 1 article<sup>18</sup> showed significant efficacy of rituximab.

**Table 1.** Complete Remission (CR) Rates after *H. pylori* Eradication in Patients with Low-grade MALT Lymphomas

Authors	n	CR (%)	Median follow up (months)
Martinelli <i>et al.</i> <sup>18</sup>	26	46.0	33.0
de Mascarel <i>et al.</i> <sup>6</sup>	60	46.7	10.0
Fischbach <i>et al.</i> <sup>16</sup>	90	62.0	44.6
Todorovic <i>et al.</i> <sup>8</sup>	34	64.7	60.0
Nakamura <i>et al.</i> <sup>9</sup>	86	65.1	42.2
Nakamura <i>et al.</i> <sup>12</sup>	73	75.0	37.0
Wündisch <i>et al.</i> <sup>14</sup>	120	80.0	75.0
Chen <i>et al.</i> <sup>15</sup>	30	80.0	10.0
Hong <i>et al.</i> <sup>13</sup>	90	94.4	45.0

MALT, mucosa-associated lymphoid tissue.



**Fig. 1.** (A) Endoscopy images of a low-grade MALT lymphoma lesion at the upper gastric corpus mucosa in a 46-year-old female patient obtained 1 month after *H. pylori* eradication, showing a nodular lesion whose surface contains patchy red spots on a discolored background. (B) Endoscopy image of the regressed low-grade MALT lymphoma lesion at the upper gastric corpus mucosa obtained 22 months after *H. pylori* eradication. (C) Histopathology image (H&E stain) of a low-grade MALT lymphoma lesion at the upper gastric corpus mucosa 1 month after *H. pylori* eradication. Small lymphoma cells infiltrated the gastric glands to form lymphoepithelial lesions ( $\times 20$  objective lens). (D) Histopathology image (H&E stain) of the regressed low-grade MALT lymphoma lesion at the upper gastric corpus mucosa obtained 22 months after *H. pylori* eradication. Lymphoma cells had disappeared, with only partial mononuclear cell infiltrates remaining ( $\times 20$  objective lens).

### 1. *Helicobacter pylori* eradication

*H. pylori* eradication therapy was followed by complete remission (CR) of low-grade gastric MALT lymphoma in 46-94% of the patients (Table 1).<sup>6,8,9,12-16,18</sup> Representative upper gastrointestinal (GI) endoscopic images of a 46-year-old female patient are shown in Fig. 1. Significant regression of the nodular and reddish colored low-grade MALT lymphoma lesion observed in the upper gastric corpus mucosa (Fig. 1A, one month after the *H. pylori* eradication) was noted at 22 months after the *H. pylori* eradication therapy (Fig. 1B). Histologically, characteristic lymphoepithelial lesion (LEL) identified in the upper gastric corpus one month after the eradication (Fig. 1C) disappeared 22 months after the *H. pylori* eradication (Fig. 1D).

Gastric lymphomas are usually staged by endoscopic ultrasonography, according to the modified Ann Arbor staging system by Musshoff and Radaszkiewicz *et al.*<sup>19</sup> Here, "E" means primary extranodal site. Stage E-I means the localized involvement of one or more GI sites on one side of the diaphragm without lymph node infiltration. Stage E-I is further characterized as E-I<sub>1</sub> (lymphoma confined to mucosa and submucosa) or as E-I<sub>2</sub> (lymphoma extending beyond submucosa). Stage E-II means the localized involvement of one or more GI sites on one side of the diaphragm with lymph node infiltration (any depth of lymphoma infiltration into the gut wall). Stage E-II is further characterized as E-II<sub>1</sub> (infiltration of regional lymph nodes) or as E-II<sub>2</sub> (infiltration of lymph nodes beyond regional area). Then, stage E-III means the localized involvement of the GI tract and/or lymph nodes on both sides of the diaphragm and stage E-IV means the localized GI bulk of lymphoma with or without infiltration of associated involvement of non-GI tract organs or tissues.

According to a prospective multicenter study conducted in Germany and Austria by Fischbach *et al.*<sup>16</sup> on 95 patients with newly diagnosed MALT lymphoma, the long-term outcome (median follow-up; 45 months) after *H. pylori* eradication was characterized by CR in 56 patients (62%), minimal residual disease (MRD) in 17 patients (18%), and partial remission (PR) in 11 patients (12%). In this study, the regression rate was higher in patients with stage E-I<sub>1</sub> disease as compared with that in those with stage E-I<sub>2</sub> disease, as diagnosed by endoscopic ultrasonography (EUS).<sup>16</sup> Wündisch *et al.*<sup>14</sup> also reported the long-term outcomes of 120 patients with gastric MALT lymphoma (stage E-I) after *H. pylori* eradication; they reported a CR of 80% and a relapse rate of only 3%. In their study,<sup>14</sup> both t(11;18)(q21;q21) translocation and

ongoing B-cell monoclonality were associated with a significantly higher risk of no response or relapse, but they were also encountered in patients showing CR. In 2006, Hong *et al.*<sup>13</sup> reported a high CR rate (94%) of gastric low-grade MALT lymphoma after *H. pylori* eradication, with a median interval to CR of 3 months.

Patients with minimally persisting lymphoma infiltrates after successful *H. pylori* eradication are considered as treatment failures and referred for further treatment. However, according to the report by Fischbach *et al.*<sup>10</sup>, most patients with minimal histological residuals after successful eradication had a favorable disease course without anti-cancer treatment, suggesting that a watch-and-wait strategy with regular follow up endoscopies and biopsies may be safe and preferred approach in the management of these patients.

In Taiwan,<sup>15</sup> two multicenter prospective studies of *H. pylori* eradication for early-stage gastric lymphoma, one for low-grade MALT lymphoma, and one for high-grade transformed tumors (diffuse large B-cell lymphoma [DLBCL] with features of MALT), were directly compared. In this study, *H. pylori* was successfully eradicated in 97% of *H. pylori*-positive low-grade lymphoma patients and 92% of *H. pylori*-positive high-grade lymphoma patients, resulting in CR in 80% and 64% of the patients in the two groups, respectively. After a median follow-up of more than 5 years of the complete responders, tumor recurrence was observed in 13% of the patients with low-grade tumors, but none of the patients with the high-grade tumors, suggesting that anti-*H. pylori* therapy is considered as one of the treatment options even for early-stage *H. pylori*-positive gastric DLBCL.<sup>15</sup>

Todorovic *et al.*<sup>8</sup> reported that in patients of primary gastric MALT lymphoma with a median follow-up duration of 5 years, the CR was 65% (22/34) and PR was 27% (9/34) after *H. pylori* eradication, and that the predictive factors for overall survival were the international prognostic index (IPI) score, blood hemoglobin level, erythrocyte sedimentation rate (ESR), and platelet count. Nakamura *et al.*<sup>9</sup> reported that patients with gastric MALT lymphomas responsive to *H. pylori* eradication therapy had a good prognosis (CR rate: 65%, 56/86), and that in non-responders to the eradication, second-line treatments resulted in CR. However, especially in the case of non-responders to *H. pylori* eradication therapy who decline second-line treatment, careful follow-up is necessary to detect development of gastric adenocarcinoma and disease progression.

*Helicobacter heilmannii* is also known as another bacterial pathogen associated with the development of gastritis and gastric MALT lymphoma.<sup>20,21</sup> According to the report by

Joo *et al.*<sup>11</sup>, although *H. heilmannii*-associated gastritis is uncommon and milder than *H. pylori*-associated gastritis, the association may be worthy of note with respect to the development of MALT lymphoma.

In regard to *H. pylori*-negative cases, according to the report by Nakamura *et al.*<sup>12</sup>, although *H. pylori*-negative gastric MALT lymphoma is characterized by a high frequency of t(11;18)(q21;q21)<sup>22</sup> and may require additional strategies other than antibiotics, 2 of 7 (29%) *H. pylori*-negative patients also responded to antibiotic treatment.

Gastric MALT lymphomas with the *API2-MALT1* fusion is generally known as resistant to *H. pylori* eradication therapy. A recent study demonstrated the clinical activity of the monoclonal antibody to CD20, rituximab in gastric MALT lymphoma patients with the *API2/MALT1* fusion.<sup>18</sup> In their study,<sup>18</sup> 46% of the patients showed pathological and clinical CR, and 31% showed a partial response, with only two patients presenting with relapse at 26 and 14 months after weekly rituximab treatment, respectively. This finding suggests that the t(11;18)(q21;q21) translocation may not, after all, be a predictive marker of response or of subsequent relapse following rituximab therapy.<sup>18</sup>

On the other hand, some gastric MALT lymphomas that are negative for the *API2-MALT1* fusion may show resistance to *H. pylori* eradication therapy. These tumors have not been well-characterized and the precise clinicopathological features are still unknown. Further studies regarding other chromosomal translocations and other bacterial infections that might be involved in the pathogenesis of gastric MALT lymphomas are necessary.

## 2. Chromosomal translocations in gastric MALT lymphoma (Table 2)

As mentioned above, gastric MALT lymphomas are characterized not only by regression in response to *H. pylori* eradication therapy,<sup>3</sup> but also by chromosomal translocations.<sup>23</sup> The *API2-MALT1* fusion that results from chromosome translocation t(11;18)(q21;q21) has been reported to be a predictor of non-responsiveness to *H. pylori* eradication therapy.<sup>22</sup> It has been suggested that since *API2-MALT1* fusion transcripts might promote survival of the MALT lymphomas by producing inhibition of apoptosis, they help in the survival of MALT lymphomas.<sup>24,25</sup>

On the other hand, t(1;14)(p22;q32) occurs in 1-2% of MALT lymphomas and has been detected in the stomach, salivary glands, intestines, and lungs.<sup>26</sup> The *BCL10* gene was isolated from the breakpoint of the t(1;14) translocation, with deregulated expression of *BCL10* in the MALT lymphomas.<sup>27,28</sup> *BCL10* activates nuclear factor

kappa B (NF- $\kappa$ B), a transcription factor for several survival-related genes, via interaction with a *MALT1* gene product.<sup>29</sup> Moreover, recent studies have shown that the *API2-MALT1* fusion protein activates NF- $\kappa$ B and is associated with nuclear *BCL10* expression.<sup>29,30</sup> Thus, some chromosomal translocations involving the *API2-MALT1* fusion promoting tumor cell survival and deregulation of *BCL10* activating several survival genes have been reported in MALT lymphomas.

## 3. Gene expression profiles of gastric MALT lymphomas (Table 2)

Recent studies using microarray analyses have revealed the gene expression profiles of gastric MALT lymphomas. Mueller *et al.*<sup>20</sup> reported increased expression of genes previously to be associated with malignancies, including *laminin receptor-1* and *MDR-1*, in LELs, and increased expression of calgranulin A/Mrp-8 in destructive LELs and malignant lymphomas. Thus, they suggest that the gene expression profiles only represent the histopathological stages of MALT lymphomas. Huynh *et al.*<sup>31</sup> also reported the gene expression signatures in gastric MALT lymphomas. Several surface markers of hematopoietic cells, such as CD1c, CD40, CD44, CD53, CD83, CD86 and members of the HLA-D family, were found to be upregulated in MALT lymphomas. Since MALT lymphomas typically exhibit the following immunophenotype-CD19(+), CD20(+), CD21(+), CD79a(+), CD5(-), CD10(-), CD23(-), and cyclin D1(-), the gene expression profile does not simply reflect a higher B-cell component, but also the antigen-dependent survival of the lymphoma cells.

MicroRNAs (miRNAs) are small non-coding RNAs that can downregulate various target genes, including tumor-associated genes. Recent studies have demonstrated that aberrant expression of miRNAs plays critical roles in the development of human malignancies.<sup>32</sup> Lu *et al.*<sup>33</sup> have reported that miRNA expression profiles can be used to classify the developmental lineages and differentiation stages of tumors. Interestingly, miRNA expression profiles are more accurate for tumor classification than conventional mRNA profiles. We recently demonstrated overexpression of hematopoietic-specific miRNAs and oncogenic miRNAs in gastric MALT lymphomas with the *API2-MALT1* fusion, and proposed that the miRNA expression profiles could be novel biomarkers and therapeutic targets for gastric MALT lymphomas.<sup>34,35</sup>

## 4. Aberrant DNA methylation in gastric MALT lymphomas (Table 2)

Since epigenetic alterations, such as DNA methylation,

**Table 2.** Molecular Alterations in Gastric MALT Lymphomas

Molecular events	Alterations in gastric MALT lymphoma	References
Chromosomal translocations	t(11;18)(q21;q21); <i>API2-MALT1</i> fusion	22, 24, 25
Alterations in gene expression	t(1;14)(p22;q32); deregulated expression of <i>BCL10</i>	26, 27, 28
	Increased expression of <i>laminin receptor-1</i> , <i>MDR-1</i> , and <i>calgranulin A/Mrp-8</i>	20
	Increased expression of <i>CD1c</i> , <i>CD40</i> , <i>CD44</i> , <i>CD53</i> , <i>CD83</i> , <i>CD86</i> , and members of the HLA-D family	31
Epigenetic alterations	Overexpression of hematopoietic-specific miRNAs and oncogenic miRNAs	34, 35
	Aberrant DNA methylation of <i>p16/INK4a</i>	36
	Aberrant DNA methylation of <i>p16/INK4a</i> and <i>p57/KIP2</i>	37
	Aberrant DNA methylation of <i>p15</i> , <i>p16</i> , <i>p73</i> , <i>hMLH1</i> , <i>DAPK</i> , <i>MINT1</i> , <i>MINT2</i> , and <i>MINT31</i>	38

MALT, mucosa-associated lymphoid tissue.

are known to be involved in the initiation and development of human malignancies, determination of the DNA methylation status might be a powerful tool for the diagnosis and treatment of malignancies.

Methylation of the *p16/INK4a* gene was observed in 60% of MALT lymphomas, however, the *p16* gene methylation status was not correlated with the presence of *API2-MALT1* fusion or any other clinicopathological factors, suggesting that aberrant methylation of the *p16* gene might be an early event in MALT lymphomagenesis.<sup>36</sup> Min *et al.*<sup>37</sup> also demonstrated methylation of *p16/INK4a* and *p57/KIP2* in 41.7 and 29.2%, respectively, of low-grade MALT lymphomas, respectively. Determination of the methylation profiles of 8 CpG islands, including *p15*, *p16*, *p73*, *hMLH1*, *DAPK*, *MINT1*, *MINT2*, and *MINT31*, revealed that *H. pylori*-dependent MALT lymphomas showed more than 4 methylated genes, while non *H. pylori*-dependent cases showed less than 2 methylated genes, indicating that *H. pylori*-dependent and non *H. pylori*-dependent gastric MALT lymphomas may have a different pathogenesis, including the aberrant DNA methylation pattern.<sup>38</sup>

Thus, aberrant DNA methylation plays critical roles in the pathogenesis of gastric MALT lymphomas and detection of the DNA methylation pattern may hold promise as a clinical tool for surveillance of gastric MALT lymphomas.

## SUMMARY

Although numerous reports have suggested a good prognosis of gastric low-grade MALT lymphomas after *H. pylori* eradication, for cases not responsive to antibiotic therapy, further molecular characterization is necessary to

establish the most suitable therapeutic strategy, including additional second-line treatment or a watch and wait policy. Molecular events associated with gastric MALT lymphomas such as chromosomal translocations, altered gene expressions and epigenetic modifications (Table 2) might provide predictive information for therapeutic responsiveness as well as for recurrence or relapse of the disease. Large-scale cohort studies with molecular examinations should be performed to establish the therapeutic strategies for gastric MALT lymphomas after the successful *H. pylori* eradication.

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