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***Helicobacter pylori*-negative gastric mucosa-associated lymphoid tissue lymphomas: A review**

Asano N *et al*. *H. pylori*-negative gastric MALT lymphomas

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**Abstract**

Since Isaacson and Wright first reported on the extra-nodal marginal zone B-cell lymphoma of the stomach in 1983, following studies have clarified many aspects of this disease. We now know that the stomach is the most affected organ by this disease, and approximately 90% of gastric mucosa-associated lymphoid tissue (MALT) lymphomas are related to *Helicobacter pylori* (*H. pylori*) infection. This implies that approximately 10% of gastric MALT lymphomas occur independent of *H. pylori* infection. The pathogenesis of these *H. pylori*-negative gastric MALT lymphomas remains unclear. To date, there have been several speculations. One possibility is that genetic alterations result in nuclear factor-kappa B (NF-κB) activation. Among these alterations, t(11;18)(q21;q21) is more frequently observed in *H. pylori*-negative gastric MALT lymphomas, and such translocation results in the synthesis of fusion protein API2-MALT1, which causes canonical and noncanonical NF-κB activation. Another possibility is infection with bacteria other than *H. pylori*. This could explain why *H. pylori* eradication therapy can cure some proportions of *H. pylori*-negative gastric MALT lymphoma patients, although the bacteria responsible for MALT lymphomagenesis are yet to be defined. Recent advances in endoscopy suggest magnifying endoscopy with narrow band imaging as a useful tool for both detecting gastric MALT lymphoma lesions and judging the response to treatment. A certain proportion of *H. pylori*-negative gastric MALT lymphoma patients respond to eradication therapy; hence, *H. pylori* eradication therapy could be considered as a first-line treatment for gastric MALT lymphomas regardless of their *H. pylori* infection status.

**Key words:** *Helicobacter pylori*; Mucosa-associated lymphoid tissue lymphoma; API2-MALT1; Antibiotics; Endoscopy

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**Core tip:** Although the majority of gastric mucosa-associated lymphoid tissue (MALT) lymphoma patients are infected with *Helicobacter pylori* (*H. pylori*), approximately 10% of patients do not have *H. pylori* infection. Recent studies have demonstrated that eradication therapy for *H. pylori* is effective not only for *H. pylori*-positive but also for *H. pylori*-negative gastric MALT lymphoma patients.

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**INTRODUCTION**

Mucosa-associated lymphoid tissue (MALT) lymphoma is an extra-nodal B-cell lymphoma that arises in MALT, which was first reported by Isaacson and Wright in 1983[1]. The following studies have elucidated many aspects of this disease.

The stomach is one of the most affected organs by this disease, and approximately 90% of the affected stomachs are infected with *Helicobacter pylori* (*H. pylori*)[2].

This implies that approximately 10% of gastric MALT lymphomas occur independent of *H. pylori* infection. These gastric MALT lymphomas were considered to be resistant to *H. pylori* eradication. Although there were reports of *H. pylori*-negative gastric MALT lymphomas that were successfully treated with antibiotic therapy[3,4], there were people who assumed that those were only false negative cases[5]. We now know that some proportions of gastric MALT lymphoma in *H. pylori*-uninfected stomachs can be successfully treated with antibiotic therapy[3]. However, there are not as many reports on *H. pylori*-uninfected MALT lymphomas compared with the infected ones. Therefore, in this review, we will summarize the current knowledge of *H. pylori*-negative gastric MALT lymphomas.

**PATHOGENESIS**

The pathogen in *H. pylori*-infected cases of gastric MALT lymphomas is clearly *H. pylori*. This statement is supported by the fact that approximately 75% of *H. pylori*-positive gastric MALT lymphomas achieve complete remission (CR) by eradication of this bacterium alone[6,7] (Table 1). Chronic *H. pylori* infection attracts lymphoid cells to the gastric MALT, where these cells are continuously stimulated by *H. pylori* and give rise to MALT lymphomas. Previous studies have demonstrated that not only B cells, but also T cells and macrophages play an important role in this lymphomagenesis[8-10].

Because *H. pylori*-negative gastric MALT lymphoma patients are not infected with *H. pylori*, this bacterium cannot be responsible for the lymphomagenesis. To date, there have been several opinions regarding the pathogenesis of *H. pylori*-negative gastric MALT lymphomas.

Several genetic alterations have been identified in gastric MALT lymphomas: t(11;18)(q21;q21)*,* t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14)(p13;q32)[11, 12]. Among these genetic abnormalities, t(11;18)(q21;q21) is the most frequently detected translocation in gastric MALT lymphomas[11-14]. This translocation fuses the N-terminus of the *API2* gene to C-terminus of the *MALT1* gene, which results in the synthesis of an API2-MALT1 fusion protein[15]. *MALT1* was first reported in 1999 by two groups, and they both suggested that *API2-MALT1* is important to the pathogenesis of gastric MALT lymphomas[16,17]. The following studies revealed that API2-MALT1 fusion protein activates nuclear factor-kappa B (NF-κB) through noncanonical pathway by inducing the proteolytic cleavage of NF-κB-inducing kinase (NIK), resulting in deregulated NIK activity and noncanonical NF-κB activation[18] (Figure 1 left panel). Conversely, Zhou *et al*[19] reported that API2-MALT1 chimeric protein causes canonical NF-κB activation via deregulated ubiquitin ligase activity, which increases K63-polyubiquitination of NEMO, and Lucas *et al*[20] reported that heterotopic API2-MALT1 oligomerization and binding of TNF receptor associated factor 2 (TRAF2) are required for maximal NF-κB activation. Recent report detailed the role of RIP1 ubiquitination, resulting from TRAF2 recruitment to API2-MAT1, as necessary for full NF-κB activation[21] (Figure 1 right panel). This deregulated activation of NF-κB induces tumorigenesis[22]; therefore, this genetic alteration could be a cause of *H. pylori*-negative gastric MALT lymphoma.

Some groups suspected the involvement of a bacterium other than *H. pylori*. Indeed, there are several bacteria and viruses identified to have a correlation between marginal zone B cell lymphomas (*Campylobacter jejuni* and immunoproliferative small intestinal disease, *Borellia burgdorferi* and primary cutaneous B-cell lymphoma, *Chlamydophila psittaci* and ocular adnexal lymphoma, hepatitis C virus and splenic marginal zone lymphoma)[23], and it is possible that bacteria other than *H. pylori* are causing chronic inflammation in the stomachs of *H. pylori*-negative gastric MALT lymphoma patients. Morgner *et al*[24] reported 5 cases of *H. pylori*-negative but *H. heilmannii*-positive gastric MALT lymphomas. These patients were treated with 40 mg omeprazole and 750 mg amoxicillin 3 times per day for 14 d, which is a similar treatment to *H. pylori* eradication, and the eradication of this bacterium resulted in CR in all 5 patients. *H. heilmannii* infection causes gastric B-cell lymphomas in mice[25], hence gastric infection by this bacterium may be a cause of *H. pylori*-negative gastric MALT lymphomas. Nonetheless, bacteria that have not yet been identified may be involved in this MALT lymphomagenesis, and further studies are warranted to clarify the details.

Another possibility is the involvement of autoimmune diseases. Sjögren’s syndrome is associated with an increased risk for parotid gland MALT lymphomas[26], and a meta-analysis reported that the odds ratio of MALT lymphoma development for Sjögren’s syndrome was 18.8 (95% CI: 9.5-37.3)[27]. Hashimoto’s thyroiditis is also a known risk factor for thyroid lymphoma[28]. Therefore, we cannot deny the possibility that autoimmune diseases are also involved in gastric MALT lymphomagenesis, and further investigations are warranted.

**DIAGNOSIS**

Because the clinical symptoms of gastric MALT lymphomas are usually non-specific[29], gastric MALT lymphoma lesions are traditionally detected by screening esophagogastroduodenoscopy. Gastric MALT lymphoma lesions of *H. pylori*-negative subjects are similar to those observed in *H. pylori*-positive subjects[30]. Their endoscopic findings are classified as the superficial-spreading type, mass-forming type, diffuse infiltrating type and unclassified[31, 32]. Many gastric MALT lymphoma lesions have similar endoscopic findings to early gastric cancers, but the discrimination between them is critical because the treatment for these diseases is different. Among these, the superficial-spreading type is most sensitive to antibiotic therapy[6].

The depth of the affected lesion is evaluated by endoscopic ultrasonography. Depth evaluation is important because gastric MALT lymphomas with deep submucosal invasions respond less to eradication therapy[33].

A definitive diagnosis for gastric MALT lymphomas is made by histopathology. Histological scoring of lymphoid infiltrations in the stomach according to Wotherspoon *et al*[34] has been broadly used for histopathological evaluation. It is important to perform an adequate number of biopsies from the lesions both for making an accurate diagnosis and ruling out the possibility of diffuse large B cell lymphomas, and Fischbach proposed that at least ten biopsies are required[35]. In addition to histopathology, immunostaining for B-cell markers can aid in diagnosis[36].

Genetic alterations that are observed in MALT lymphomas can be helpful for diagnosing the disease and for predicting the response to antibiotic therapy as mentioned below. The presence or the absence of these alterations can be diagnosed by reverse transcription polymerase chain reaction or by fluorescence in situ hybridization[36].

Clinical staging of gastric MALT lymphomas is defined according to either the Lugano international conference classification[37] or the modified Ann Arbor staging system[36]. The former is mainly based on radiological findings, whereas the latter takes the depth of gastric wall infiltration into consideration. Because depth of the affected lesion correlates with antibiotic therapy responsiveness[33], the latter may reflect the prognosis better than the former, but validation by prospective studies are warranted.

There are a number of methods for the diagnosis of *H. pylori* infection[38]. It is always important to combine different methods together, usually combining a non-invasive and an invasive method (*e.g.*, urea breath test and histopathology), to exclude the possibility of a false-negative result. We must also be aware of the possibility of a pseudo-negative result in patients with extreme gastric mucosal atrophy and patients taking proton-pump inhibitors (PPI).

Recently, the usefulness of magnifying endoscopy in detecting gastrointestinal lesions has been given attention[39], and magnifying endoscopy with narrow-band imaging (MNBI) is proposed to be a useful technique to diagnose gastric MALT lymphomas[32, 40, 41]. Interestingly, Nonaka *et al*[41] reported that MNBI was useful in not only detecting gastric MALT lymphomas but also in evaluating their response to eradication therapy. This additional information is very helpful because it is often not easy to judge whether the patient should undergo second-line therapy after *H. pylori* eradication therapy in *H. pylori*-negative gastric MALT lymphomas.

**TREATMENT**

All of the gastric MALT lymphoma patients are considered to have an indication for antibiotic treatment regardless of their clinical stages[36, 42]. Standard antibiotic therapy consists of a combination of amoxicillin, clarithromycin and PPI[43]. According to previous reports, approximately 75% of *H. pylori*-positive gastric MALT lymphomas are successfully treated by the eradication of this bacterium[6,7]. However, due to the increasing drug resistance of *H. pylori*, many alternative therapies are proposed, such as the therapy adopting metronidazole instead of clarithromycin[44].

The first-line treatment for *H. pylori*-negative gastric MALT lymphomas is also antibiotic therapy[36]. Even in the absence of *H. pylori* infection, several studies have reported that certain proportions of patients responded to this antibiotic therapy[3,4,14,30,45-52] (Table 2).

Raderer *et al*[4]reported that five out of six *H. pylori*-negative gastric MALT lymphoma patients responded to antibiotic therapy (one had partial remission and four had complete remission), which corresponds to an excellent response rate of 83%. This was the highest reported response rate among *H. pylori*-negative gastric MALT lymphomas. The response rate decreased to 46% in their later study[52], but this was still relatively high compared with other reports[3,46-50]. Contrary to these reports, earlier studies reported that *H. pylori*-negative gastric MALT lymphomas did not respond to antibiotic therapy[14,30,45]. One possible explanation for this discrepancy could be the insufficient time span between antibiotic therapy and the judgment of the treatment. For example, Ye *et al*[14] judged the antibiotic treatment as not effective at the median time of 7.5 months (range: 4-12 mo). However, the median time span to reach complete remission after antibiotic therapy was 6 mo in our study, and we experienced a number of cases that took 24 mo or longer to reach remission[47]. Raderer *et al*[52] also noted that, although most of the patients responded to antibiotic therapy in 3-9 mo, they did experience a case that took 36 mo to achieve complete remission. Nonetheless, further studies are warranted to clarify the cause underlying this discrepancy.

Regarding the predictive factor for responsiveness, multiple lesions[49], lesions in both proximal and distal parts of the stomach[50], and the presence of t(11;18)(q21;q21)[50] were predictive factors for non-responsiveness to antibiotic therapy. We have previously reported that 5 out of 17 *H. pylori*-negative gastric MALT lymphoma patients treated with antibiotics and PPI responded to the therapy, and 3 out of 5 responders had single lesions, while all non-responders had multiple lesions[49]. Similarly, Choi *et al*[50] reported that non-responders had lesions in both proximal and distal parts of the stomach, although they did not distinguish patient *H. pylori* infection status (2 out of 40 in responders, 4 out of 15 in non-responders). Regarding the t(11;18)(q21;q21) translocation, 2 out of 3 *H. pylori*-negative patients without this translocation were indicated to have responded to antibiotic therapy, while the remaining patient with this translocation did not[50]. Other studies also reported that gastric MALT lymphoma patients with t(11;18)(q21;q21) are more resistant to antibiotic therapy[6, 12]. Because this translocation is more frequently observed in *H pylori*-negative gastric MALT lymphoma patients[12,14], this needs to be taken into consideration.

The reason why *H. pylori*-negative gastric MALT lymphomas respond to antibiotic therapy is not clear, but there are several possible speculations.

One speculation, as mentioned above, is that these patients were infected with bacteria other than *H. pylori*, and the antibiotic eradication therapy for *H. pylori* was able to eradicate this non-*H. pylori* bacteria[24].

Another explanation is that clarithromycin (included in the eradication medication) affected the patients’ immune system through its immunomodulatory effect[53,54]. Nevertheless, further studies are warranted to elucidate the mechanisms involved in this reaction.

Previously, when antibiotic therapy was considered ineffective, radiotherapy was used as the first-line therapy for *H. pylori*-negative gastric MALT lymphomas[55]. Gastric MALT lymphomas are sensitive to radiotherapy, and, according to Zullo *et al*[56], 97.8% of patients who were resistant to antibiotic therapy responded to radiotherapy. Chemotherapy efficiency for these patients has also been described[56], and a combination of anti-CD20 monoclonal antibodies with chemotherapy reportedly gives promising results[57,58].

However, currently there is no consensus for the patients who did not respond to antibiotic therapy. Because the disease is indolent by nature, and because complications are possible[59,60], a ‘watch-and-wait’ strategy may be efficient for these patients if they do not have progressive disease[2, 36, 52].

**CONCLUSION**

Recent studies on *H. pylori*-negative gastric MALT lymphomas have suggested that *H. pylori* eradication therapy is effective in some proportion of patients with this disease and could be considered as a first-line treatment.

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**Figure 1 API2-MALT1 fusion protein induces noncanonical and canonical nuclear factor-kappa B activation.**

**Table 1 Comparison of *Helicobacter pylori*-positive and *Helicobacter pylori-*negative gastric mucosa-associated lymphoid tissue lymphomas**

|  |  |  |
| --- | --- | --- |
|  | ***H. pylori*-positive** | ***H. pylori*-negative** |
| Pathogenesis | *H. pylori* infection | Genetic alterationsOther bacterial infectionAutoimmune diseases |
| First-line therapy | Antibiotic therapy | Antibiotic therapy |
| Response rate for antibiotic therapy | 75% | 28%  |

*H. pylori*: *Helicobacter pylori*.

**Table 2 Previous reports on** ***Helicobacter pylori*-negative gastric mucosa-associated lymphoid tissue lymphomas *n* (%)**

|  |
| --- |
| **Responding patients/ treated patients (responding rate)** |
| Steinbach *et al* (1999)[45]  | 0/6 (0) |
| Ruskone-Fourmestraux *et al* (2001)[30] | 0/10 (0) |
| Ye *et al* (2003)[14] | 0/5 (0) |
| Nakamura *et al* (2006)[3]  | 2/7 (29) |
| Raderer *et al* (2006)[4]  | 5/6 (83) |
| Akamatsu *et al* (2006)[46]  | 1/9 (11) |
| Terai *et al* (2008)[47] | 1/4 (25) |
| Park *et al* (2010)[48] | 3/4 (75) |
| Asano *et al* (2012)[49] | 5/17 (29) |
| Choi *et al* (2013)[50] | 2/5 (40) |
| Raderer *et al* (2015)[52]  | 5/13 (46) |