Eradication Therapy Is Effective for Helicobacter pylori-Negative Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

Naoki Asano, Katsunori Iijima, Shiho Terai, Xiaoyi Jin, Nobuyuki Ara, Takashi Chiba, Jun Fushiya, Tomoyuki Koike, Akira Imatani and Tooru Shimosegawa

1 Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

Mucosa-associated lymphoid tissue (MALT) lymphomas are extra-nodal B-cell lymphomas arising from MALT, and the most commonly affected organ is the stomach. Helicobacter pylori (H. pylori) eradication therapy with proton-pump inhibitors and antibiotics is the first-line therapy for H. pylori-positive gastric MALT lymphomas, but the effectiveness of the therapy for H. pylori-negative gastric MALT lymphomas remains controversial. Hence, we aimed to evaluate the effectiveness of this eradication therapy for H. pylori-negative MALT lymphomas. The H. pylori infection status of 158 gastric MALT lymphoma patients followed in our unit was judged by urea breath test, rapid urease test, histology of the biopsy specimen taken from the stomach during endoscopy, and serum antibody against H. pylori. Seventeen patients that were negative for all four tests and did not have gastric mucosal atrophy were treated with antibiotic eradication therapy. The average age at diagnosis was 56.8 years old (range: 36-73 years), and the median follow-up period after H. pylori eradication in all 17 patients was 5.3 years (range: 0.3-12.7 years). Five patients (29.4%) achieved complete remission (CR) by eradication therapy alone. Comparison between the responding and non-responding patients revealed that the patients endoscopically diagnosed to have a single lesion of gastric MALT lymphoma were seen only in the responding group, whereas all non-responding patients had multiple lesions (P < 0.05). In conclusion, H. pylori eradication therapy achieved a favorable CR rate in H. pylori-negative gastric MALT lymphoma patients and could be considered as a first-line therapy, especially for patients with a single lesion.

Keywords: antibiotics; eradication therapy; Helicobacter pylori; mucosa-associated lymphoid tissue lymphoma; predictive factor
efficacy is still controversial (Nakamura et al. 2006, 2012; Raderer et al. 2006). In this study, we intended to evaluate the efficacy of eradication therapy in patients with \textit{H. pylori}-uninfected gastric MALT lymphoma.

\textbf{Materials and Methods}

\textit{Patients and follow up}

158 histologically verified gastric MALT lymphoma patients were followed up in our division from April 1995 to May 2012. Patients were tested for \textit{H. pylori} infection by urea breath test, rapid urease test, histology of the biopsy specimen taken from the gastric body and the antrum during endoscopy, and serum antibody against \textit{H. pylori}. Twenty-one patients that were negative for all the tests were judged as \textit{H. pylori} negative. The presence of gastric mucosal atrophy was determined by endoscopic examination based on the criteria of Kimura and Takemoto as previously described (Iijima et al. 2012), and 3 of the 21 patients with endoscopic gastric mucosal atrophy were excluded, since these patients could have been previously infected with \textit{H. pylori}. As a result, 18 patients were diagnosed as \textit{H. pylori} uninfected and were included in this study. Their clinical staging was determined by upper gastrointestinal (GI) tract endoscopy, colonoscopy, bone marrow puncture, X-ray computed tomography (CT) and/or positron emitting tomography (PET), applying the Lugano staging system (Zucca et al. 1997). The chimeric transcript of t(11;18)(q21;q21) API2-MALT1 gene was investigated in 11 patients by either reverse-transcriptase polymerase chain reaction or fluorescence \textit{in situ} hybridization as previously described (Terai et al. 2008). All the patients were followed up with upper GI tract endoscopy every six months, and with X-ray CT or PET every year. MALT lymphoma was judged as CR when the absence of lymphoma was confirmed both macroscopically and pathologically in two consecutive investigations. The characteristics, treatments and outcomes of the patients were analyzed retrospectively.

\textit{Statistical analysis}

Student’s \textit{t}-test and Fisher’s exact probability tests were used to evaluate the statistical significance of the difference. \(P < 0.05\) was considered as statistically significant.

\textbf{Results}

The clinical features of the patients included in this study are shown in Table 1. The average age at diagnosis was 56.8 years old (from 36 to 73 years), and the median follow-up period after \textit{H. pylori} eradication in all 17 patients was 5.3 years (from 0.3 to 12.7 years). Sixteen patients were diagnosed as stage I, while two patients were diagnosed as stage II-1 according to the Lugano staging system. MALT lymphoma lesions were predominantly located in the gastric body (16 out of 18, 88.9%) and were endoscopically classified as the superficial type (14 out of 18, 77.8%). MALT lymphoma presented as multiple lesions in 15 of 18 patients (83.3%). t(11;18)/API2-MALT1 translocation was positive in 7 of the 11 patients

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<th>patient</th>
<th>gender</th>
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<th>location</th>
<th>endoscopic appearance</th>
<th>number of lesions</th>
<th>t(11;18)/API2-MALT1</th>
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ND, not diagnosed; CR, complete remission; NR, no response.

*: eradication therapy including metronidazole
who agreed to take the examination (63.6%).

Among the 18 H. pylori–negative patients, 17 patients were treated with H. pylori eradication therapy (Fig. 1), while one patient was treated with radiation therapy of the whole stomach (total 30 Gy) as a first-line therapy upon the patient’s request. Sixteen patients were treated with lansoprazole (60 mg/day), clarithromycin (800 mg/day), and amoxicillin (1,500 mg/day) for 7 days, and one patient was treated with lansoprazole (60 mg/day), metronidazole (500 mg/day), and amoxicillin (1,500 mg/day) for 7 days since this patient had already undergone the standard eradication regimen but did not achieve remission.

Among the 17 patients who received eradication therapy, 5 patients (29.4%), including the patient who received metronidazole, achieved complete remission with antibiotic therapy alone. Five of the patients who did not respond to the treatment received radiation therapy, and complete remission was obtained in all 5 patients (100% of the patients). The remaining 7 patients refused to undergo radiation therapy and were simply observed (watch and wait). At present, none of the watch and wait patients showed progression of their disease or transformation into diffuse large B cell lymphoma during an average observation period of 7.0 years.

Comparison between the patients that did (responders) and did not (non-responders) achieve remission with the antibiotic eradication therapy showed that there was a significant difference in the number of lesions between these groups. As shown in Table 2, a single lesion was seen in 3 of 5 responders (60%), but in none of the 12 non-respond-
ers ($P < 0.05$). In addition, antral lesions were observed in 2 of 5 responders (40%), but in none of non-responders ($P = 0.07$).

**Discussion**

It has been reported that more than 90% of gastric MALT lymphomas are *H. pylori* positive, and there are few reports on *H. pylori*-negative gastric MALT lymphomas (Weber et al. 1994; Nakamura et al. 2006). We describe 18 patients with *H. pylori*-negative gastric MALT lymphoma, who were followed up in our division for an average of 6.0 years. In this study, we excluded *H. pylori*-negative patients who had endoscopic gastric mucosal atrophy, because it is likely that these patients had *H. pylori* infection in the past and the absence of *H. pylori* is merely the consequence of extensive gastric mucosal atrophy. Hence, this study consists of patients with definitive diagnosis of *H. pylori*-negative gastric MALT lymphoma.

The location, endoscopic appearance and clinical staging of the *H. pylori*-negative MALT lymphomas did not differ from the positive lymphomas in our previous study, whereas the positive rate of t(11;18)/API2-MALT1 in *H. pylori*-negative MALT lymphomas in the present study (63.6%) was substantially higher than that in *H. pylori*-positive cases in our previous study (11.5%) (Terai et al. 2008).

The effectiveness of *H. pylori* eradication therapy against *H. pylori*-negative gastric MALT lymphomas remains controversial, but some authors have reported the antibiotic eradication therapy to be effective. Nakamura et al. (2006) reported CR was achieved in 2 out of 7 *H. pylori*-negative patients (28.6%), while Raderer et al. (2006) showed a CR rate of 83.3% (5 out of 6 patients).

A Japanese multicenter cohort follow-up study has recently reported that only 6 out of 44 *H. pylori*-negative MALT lymphoma patients achieved CR by eradication therapy alone (13.6%) (Nakamura et al. 2012). They concluded that *H. pylori*-negative status and t(11;18)/API2-MALT1 are predictive factors for resistance against *H. pylori* eradication therapy, but since their study was a multicenter study, the detailed clinical features of the patients were unclear.

In our study, we achieved CR in 5 out of 17 patients with *H. pylori* eradication therapy alone (29.4%). This CR rate was similar to that of the above mentioned report by Nakamura and colleagues (28.6%), in which the patients were all positive for t(11;18)/API2-MALT1 (Nakamura et al. 2006). Analyzing in detail, the clinical features of our patients revealed that only one patient achieved CR by eradication therapy alone when t(11;18)/API2-MALT1 was positive (patient 18, 14.3% among t(11;18)/API2-MALT1 positive patients).

On the other hand, Raderer et al. (2006) reported a high CR rate of 83.3% (5 out of 6 patients). This difference may be due to the low positive rate for t(11;18)/API2-MALT1 in their patients (16.7%), but this could also be due to differences in the antibiotics used for eradication. In Raderer’s report, they used metronidazole instead of amoxicillin, and this may have contributed to their high CR rate. We also experienced CR achieved in a patient who did not respond to the standard first-line eradication therapy and therefore received metronidazole (patient 1). In addition, previous studies reported that *H. pylori* eradication therapy was effective for *H. pylori*-negative rectal MALT lymphomas (Nakase et al. 2002; Nomura et al. 2010). These previous reports and our study suggest the possibility that microorganisms other than *H. pylori* are involved in the development of MALT lymphomas, which could account for the effectiveness of different antibiotics on *H. pylori* negative MALT lymphomas, but further studies are warranted.

Comparison between the patients that did and did not respond to the antibiotic eradication therapy showed that solitary lesions were only detected in the responders and that this difference was statistically significant. This finding suggests that evaluating the number of lesions may be useful for predicting the efficacy of eradication therapy against *H. pylori*-negative gastric MALT lymphoma patients, concerning which this is the first report. On the other hand, some predictive factors for successful eradication therapy against *H. pylori*-positive gastric MALT lymphomas have been previously reported (Ruskoné-Fournestraux et al. 2001; Isaacson 2005). The location of the lesion is one of the factors associated with efficacy. Kim et al. (2007) have reported that in *H. pylori*-infected gastric MALT lymphoma patients, those with distal lesions had higher CR rates (92.5%) than those with proximal lesions (CR rate 65.5%). We also observed the same tendency in *H. pylori*-negative MALT lymphoma patients, among whom only the responders had antral lesions, but this tendency did not show statistical significance due to the limited number of patients. Further studies with larger numbers of patients are warranted to verify this tendency.

All the patients who underwent radiation therapy in our study were able to achieve CR. This proved that radiation therapy is a very promising therapy for *H. pylori*-negative MALT lymphomas that is resistant to eradication therapy. However, we experienced a case of signet-ring cell gastric cancer that was possibly related to radiation for *H. pylori*-negative MALT lymphoma (Asano et al. 2011). Since gastric MALT lymphomas are a slowly progressing disease and since no patient had disease progression in our watch and wait follow up, eradication therapy including multiple antibiotics may be worth trying before proceeding to radiation therapy.

In conclusion, our analysis suggested that *H. pylori* eradication therapy is an effective first-line therapy for *H. pylori*-negative gastric MALT lymphomas, and that the patients with a single lesion are more likely to respond to this therapy. In addition, multiple regimens using different antibiotics could be a potential second-line therapy.
Eradication Therapy for *H. pylori*-Negative MALT Lymphomas

**Conflict of Interest**

The authors have no conflict of interest.

**References**


