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BRIEF ARTICLE

Treatment outcome of localized *Helicobacter pylori*-negative low-grade gastric MALT lymphoma

Hyung Soon Park, Yu Jin Kim, Woo Ick Yang, Chang Ok Suh, Yong Chan Lee

Hyung Soon Park, Yu Jin Kim, Yong Chan Lee, Department of Internal Medicine, Yonsei University College of Medicine, 120-752 Seoul, South Korea
Woo Ick Yang, Department of Pathology, Yonsei University College of Medicine, 120-752 Seoul, South Korea
Chang Ok Suh, Department of Radiation Oncology, Yonsei University College of Medicine, 120-752 Seoul, South Korea
Author contributions: Park HS analyzed the data and wrote the manuscript; Yang WI performed the histopathological analysis; Suh CO and Lee YC designed the study; Kim YJ and Lee YC edited and reviewed the manuscript.
Correspondence to: Yong Chan Lee, MD, PhD, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, 120-752 Seoul, South Korea. leeyc@yuhs.ac
Telephone: +82-2-22281960 Fax: +82-2-3936884
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Abstract

AIM: To investigate treatment outcome of *Helicobacter pylori* (*H. pylori*)-negative low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

METHODS: In this study, we retrospectively reviewed the clinical outcome and clinicopathologic factors of stage I E *H. pylori*-negative low-grade gastric MALT lymphoma cases from August 1998 to June 2009.

RESULTS: A total of eleven patients with *H. pylori*-negative low-grade gastric MALT lymphoma were enrolled in the study and received anti-*H. pylori* eradication treatment and/or radiotherapy or excisional therapy. Complete remission (CR) of gastric MALT lymphoma was achieved in all patients. The time to CR was 1-66 mo (median, 1 mo).

CONCLUSION: Eradication therapy may be offered as an initial treatment option even in cases of localized *H. pylori*-negative gastric MALT lymphoma.

Key words: Anti-bacterial agents; *Helicobacter pylori*; Mucosa-associated lymphoid tissue lymphoma; Radiotherapy; Stomach

Peer reviewer: Philippe Lehours, MD, PhD, University Bordeaux 2, INSERM U853, Bat 2B RDC Zone Nord, 146 rue Léo Saignat, Bordeaux cedex, 33076, France

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INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma, first described in 1983 by Isaacson and Wright[1], has been recently re-classified as extranodal marginal zone lymphoma of MALT-type, in the Revised European-American Classification of Lymphoid Neoplasms (REAL)/World Health Organization (WHO) Classification of Lymphoid Neoplasms. An important feature of MALT lymphoma is the presence of lymphoepithelial lesions formed by the invasion of individual glands by aggregates of lymphoma cells[2].

In previous studies, *Helicobacter pylori* (*H. pylori*) infection was suggested to be causally associated with primary gastric MALT lymphoma[3,4]. Indeed, *H. pylori* provides the antigenic stimulus, which is mediated by mucosal T cells, for sustaining the growth of gastric MALT lymphoma[5]. The regression of gastric MALT lymphoma after the eradication of *H. pylori* was first reported in 1993 by Wotherspoon *et al*[3]. *H. pylori* eradication led to complete remission in 80% of stage I E, low-grade gastric MALT lymphoma patients, with a yearly recurrence rate of approximately 5%[6]. Curr-

ently, eradication of *H. pylori* is considered the accepted initial therapy in cases of localized, stage I E low-grade gastric MALT lymphoma[7].

However, there are no treatment guidelines for the management of patients who are unresponsive to antibiotic treatment or for the subset of patients who present with stage I E low-grade gastric MALT lymphoma but are *H. pylori*-negative and understandably do not respond to antibiotic treatment[8]. In these cases, treatment choices include the known, conventional therapeutic approaches such as surgery, chemotherapy or radiotherapy[9]. Because of the ambiguity of treatment in *H. pylori*-negative patients, further studies are required to clarify a treatment strategy for *H. pylori*-negative MALT lymphoma. In this study, we evaluated the treatment outcome of eleven *H. pylori*-negative low-grade gastric MALT lymphoma patients to offer therapeutic guidelines for treating *H. pylori*-negative low-grade gastric MALT lymphoma.

MATERIALS AND METHODS

Patients

We retrospectively studied eleven patients with *H. pylori*-negative low-grade gastric MALT lymphoma diagnosed at the Severance Hospital from August 1998 to June 2009. All patients were confirmed by pathology to have low-grade gastric MALT lymphoma without a diffuse large B-cell lymphoma (DLBCL) component. Histological diagnosis of MALT lymphoma was performed according to the criteria outlined in the WHO classification, and histological assessment was performed by a reference pathologist (Yang WI). Immunological phenotyping of paraffin sections was performed to demonstrate light chain restriction and the $CD20^{+}CD5^{-}CD10^{-}cyclinD1^{-}$ phenotype which was microscopically consistent with the presence of low-grade MALT lymphoma. The study was approved by our institutional review board, and informed consent was not required.

Examination of H. pylori infection and endoscopic findings

None of the patients had evidence of *H. pylori* infection as judged by histology, a urea breath test, a rapid urease test (CLO™, Delta West, Bentley, Western Austria) and serological testing. The gross phenotype for each patient was classified into five types according to endoscopic features: (1) ulcerative: one or more ulcerations; (2) protruding: elevated or polypoid; (3) granular: small nodules on the lesion; (4) infiltrative: mucosal infiltration; and (5) mixed.

Staging work-up

Determination of the stage of disease included a detailed physical examination, chest X-ray, abdominal computed tomography (CT), endoscopic ultrasonography (EUS), bilateral bone marrow examination, and ^{18}F-FDG PET scan.

Therapeutic approach

Treatment modalities included anti-*H. pylori* eradication therapy, radiotherapy, and excisional therapy (one endoscopic mucosal resection and one subtotal gastrectomy). The most common treatment was radiotherapy (six patients), followed by anti-*H. pylori* eradication only (three patients). Prior to radiotherapy, three of the six radiotherapy patients received anti-*H. pylori* eradication therapy which consisted of amoxicillin (2 × 1000 mg/d), clarithromycin (2 × 500 mg/d), and esomeprazole (2 × 40 mg/d) or pantoprazole (2 × 20 mg/d) for 7 or 14 d. Radiotherapy was performed at a total dose ranging from 30 Gy to 36 Gy on an outpatient basis. Two patients underwent local excision therapy, including one subtotal gastrectomy and one endoscopic mucosal resection (EMR).

Response assessment

The median time for follow-up after remission was 25 mo (range: 5-76 mo). Complete remission (CR) was defined as the total disappearance of clinical evidence for lymphoma and an absence of histologic evidence for lymphoma on biopsy specimens. Partial remission (PR) was defined as a tumor reduction of at least 50%, and stable disease (SD) was defined as variation within either a 50% decrease or 25% increase in tumor size. In cases with complete remission, endoscopic examinations and biopsies were performed at regular intervals.

RESULTS

Baseline characteristics

The male to female patient ratio in this study was 1:1.2. The mean age of the patients was 55.7 (36-73) years. Four patients were symptomatic at presentation indicating abdominal pain (two cases), abdominal discomfort (one case), and GI bleeding (one case). Lymphoma was most often localized in the body and the antrum in 36% of the patients. Endoscopic lesions were characterized as ulcerative (five cases), infiltrative (one case), protruding (two cases), granular (one case) and mixed (two cases). Initial endoscopic findings are summarized in Table 1. Initial clinical staging with EUS and/or CT scans and BM examinations revealed all the cases to be stage I E.

Treatment outcome

Complete remission (CR) of gastric MALT lymphoma was achieved in all patients (Table 2). The time to CR ranged from one to 66 mo (median, 1 mo). Anti-*H. pylori* eradication therapy was performed in six of the eleven patients. Three of six patients, who completed the follow-up endoscopic examination 1 or 2 mo later, had complete remission of gastric MALT lymphoma. However, two patients refused to wait for the treatment response evaluation and subsequently underwent radiotherapy for definitive treatment. The remaining patient had stable disease for 2 mo before being referred for radiotherapy. All three of these patients showed complete remission of gastric MALT lymphoma 1 mo after the cessation of radiotherapy based on histological evidence. None of the 11 patients showed

Table 1 Baseline characteristics of *H. pylori*-negative low-grade gastric MALT lymphoma *n* (%)

	H. pylori negative MALT lymphoma (*n* = 11)
Age (yr, mean)	55.7 (36-73)
Sex	
Men	5 (45)
Women	6 (55)
Site	
Cardia	1 (9)
Fundus	1 (9)
Body only	3 (27)
Body & antrum	4 (36)
Diffuse	2 (18)
Endoscopy	
Ulcerative	5 (45)
Infiltrative	1 (9)
Protruding	2 (18)
Granular	1 (9)
Mixed	2 (18)

H. pylori: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue.

Table 2 Individual characteristics of 11 cases of *H. pylori*-negative low-grade gastric MALT lymphoma

	Age (yr)/ sex	Stage	Treatment	Response	Time to CR (mo)	Follow up time after remission (mo)
Case 1	54/F	I E	Eradication	CR	1	6
Case 2	60/F	I E	Eradication	CR	1	27
Case 3	52/F	I E	Eradication	CR	2	25
Case 4	36/M	I E	RTx	CR	1	76
Case 5	58/F	I E	RTx	CR	2	17
Case 6	69/M	I E	RTx	CR	1	47
Case 7	41/F	I E	Eradication + RTx	CR	1	7
Case 8	62/M	I E	Eradication + RTx	CR	1	8
Case 9	55/M	I E	Eradication -> RTx	CR	1	5
Case 10	73/F	I E	STG	CR	66	54
Case 11	53/M	I E	EMR	CR	2	69

CR: Complete remission; RTx: Radiotherapy; STG: Subtotal gastrectomy; EMR: Endoscopic mucosal resection.

local or distant recurrence after a median follow-up time of 25 mo (range: 5-76 mo).

DISCUSSION

The prevalence of *H. pylori* in patients with low-grade gastric MALT lymphoma is variable[10]. It is possible that a reduced number of *H. pylori* organisms present in the infection may account for the negative *H. pylori* diagnostic test result in some cases, and false-negative results may also be obtained when only one diagnostic method is employed[11]. The European Guidelines generally take the gold standard to be represented by at least two tests[12]. When appropriate diagnostic methods are used, the prevalence of *H. pylori* infection in low-grade MALT lymphoma is high, at nearly 90%[10]. In our study, four diagnostic tests were performed and showed that true *H. pylori*-negative patients were included. However, additional tests, such as culture with polymerase chain reaction, would allow the detection and identification of other infective organism[13].

Due to the excellent clinical outcome of *H. pylori* eradication treatment, the eradication of *H. pylori* with antibiotics should be employed as the sole initial treatment in the localized form (confined to the stomach) of gastric MALT lymphoma[14]. However, in advanced stages with *H. pylori*-positive gastric MALT lymphoma and in *H. pylori*-negative lymphoma, definitive treatment guidelines are not yet available despite the numerous published clinical research papers[8,14,15].

Antibiotic treatment for *H. pylori*-negative gastric MALT lymphoma has been described in a limited number of patients. We collectively reviewed a series of four published studies including patients treated solely with the anti-*H. pylori* antibiotic regimen as the initial treatment for *H. pylori*-negative stage I E gastric MALT lymphoma (Table 3). A total of 31 patients were included in these studies, and ten patients (32%) were shown to respond to this treatment alone. Raderer *et al*[16] reported that five of six patients with *H. pylori*-negative gastric MALT lymphoma responded to antibiotic treatment (one partial remission and four complete remissions). However, Steinbach *et al*[17] and Ye *et al*[18] experienced a 0% response rate. In other words, marked variation in treatment response rate was noted. Nevertheless, instituting anti-*H. pylori* treatment showed satisfactory clinical outcomes and allowed for gastric preservation in a significant number of cases with *H. pylori*-negative gastric MALT lymphoma. Although seemingly contradictory, anti-*H. pylori* treatment may be advised as the first-line therapy in *H. pylori*-negative localized gastric MALT lymphoma. Unfortunately, the effectiveness of anti-*H. pylori* treatment could not be confirmed in this study, as only four out of the six patients who received the anti-*H. pylori* eradication regimen waited long enough to receive the follow-up endoscopic examination which was used to confirm the complete remission status of MALT lymphoma. The other two patients proceeded to radiation therapy due to various clinical and psychosocial issues. In addition, previous studies also included patients with advanced stages of disease, including ⅡE$_1$ (Table 3). However, it was not possible from the available data to categorize lymphoma regression according to tumor stage (I E *vs* ⅡE$_1$). Therefore, additional studies are needed to define the role of anti-*H. pylori* eradication therapy in advanced stages of gastric MALT lymphoma such as stages ⅡE, ⅢE or Ⅳ.

There is still no explanation for the effectiveness of anti-*H. pylori* treatment in *H. pylori*-negative gastric MALT lymphoma[16]. However, it has been speculated that another infective organism, *Helicobacter heilmannii*[19], might be involved in the development of gastric MALT lymphoma. Also, one cannot rule out the possibility that unknown bacterial agents capable of surviving in the stomach might play a role in the development of rare *H. pylori*-negative

Table 3 Efficacy of eradication treatment in *H. pylori*-negative gastric MALT lymphoma reported in the literature *n* (%)

Author	Yr	No. of patients	Stage	Follow-up after treatment (mo)	Response rate
Steinbach *et al*[17]	1999	6	I E	5 or more	0 (0)
Ye *et al*[18]	2003	5	I E	4-12	0 (0)
Raderer *et al*[16]	2006	6	I E	12-19	5 (83)
Stathis *et al*[23]	2009	14	I E	Not described	5[1] (35)
Ruskone-Fourmestraux *et al*[24]	2001	10	I E, II E$_1$	2-21	0 (0)
Nakamura *et al*[25]	2006	7	I E, II E$_1$	1-15	2 (29)
Akamatsu *et al*[21]	2006	9	I E, II E$_1$	6 or more	1 (11)
Terai *et al*[26]	2008	4	I E, II E$_1$	Not described	1 (25)

[1]3 presented a local relapse.

Table 4 Efficacy of radiotherapy for *H. pylori*-negative gastric MALT lymphoma reported in the literature

Author	Yr	No. of patients	Stage	Follow-up after treatment, median (mo)	Response rate (%)
Schechter *et al*[27]	1998	12	I E, II E	Not described	100
Ye *et al*[18]	2003	1[1]	I E	12	100
Akamatsu *et al*[21]	2006	12 (5[1])	I E, II E$_1$	Not described	100
Chung *et al*[22]	2009	4	I E, II E	12-39	100

[1]Failure of anti-*H. pylori* treatment as the initial therapy.

gastric MALT lymphomas[16]. Another possibility is that low bacterial counts[20] and urease-negative *H. pylori* mutant strains may escape detection by the diagnostic tests that are currently available. If this assumption is correct, one might expect the noted *H. pylori*-negative gastric MALT lymphoma patient response to broad-spectrum antibiotic therapy. Also, MALT lymphoma is to some extent an immunologically driven disease, therefore an additional hypothesis may involve the potential immunomodulatory effects of the antibiotic agents used[16].

Disease control using radiotherapy alone has been previously reported in the literature, which supports the use of a modest dose of involved-field radiotherapy for patients with stages I E-II E MALT lymphoma of the stomach without evidence of *H. pylori* infection[14]. Table 4 summarizes these previously reported cases. Including our cases, 35 of 35 cases responded to radiotherapy. One of the 35 patients reported by Akamatsu *et al*[21] had a partial remission, while the others all had a complete remission. Based on these results, it is prudent to say that radiotherapy is suitable in early stage (I E or II E) *H. pylori*-negative gastric MALT lymphoma. In addition, excisional treatments such as endoscopic mucosal resection or laparoscopic gastric resection may represent another therapeutic option in the case of localized forms of gastric MALT lymphoma in individuals who are not suitable for, or who refuse, standard therapeutic approaches[15,20,22]. In the past, surgical treatment has often been advocated to establish accurate diagnosis, staging, and management of early-stage gastric lymphoma, which has about a 90% 5-year survival rate, but leads to significant morbidity[22]. In our study, two patients received endoscopic mucosal resection and subtotal gastrectomy, respectively. There has been no local or distant recurrence during the follow-up period of 54 to 69 mo.

In our series, therapeutic measures such as anti-*H. pylori* eradication, radiotherapy and excisional therapy achieved complete remission in all cases. Nevertheless, antibiotic treatment is simple, inexpensive, less harmful and *H. pylori* negative low grade MALT lymphoma shows a favorable long-term outcome[22]. Therefore we suggest that *H. pylori* eradication therapy may be an initial treatment option for localized *H. pylori*-negative gastric MALT lymphoma. In addition, further studies on eradication therapy are required to help in the establishment of strategies for patients with localized *H. pylori*-negative gastric MALT lymphoma.

COMMENTS

Background

Eradication of *Helicobacter pylori* (*H. pylori*) is a well-accepted initial therapy in cases of localized (stage I E) low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *H. pylori* infection. However, there are no treatment guidelines for the management of *H. pylori*-negative low-grade gastric MALT lymphoma.

Research frontiers

Previous studies revealed the effectiveness of radiotherapy for localized *H. pylori*-negative low grade gastric MALT lymphoma. However, *H. pylori* eradication therapy is still a controversial treatment modality, although this treatment is simple and less harmful than other treatments.

Innovations and breakthroughs

With the exception of this study, only 31 *H. pylori*-negative patients have received eradication therapy (response rate 32%). However, treatment response was variable. The authors' study enrolled a small number of patients, but they all had complete remission.

Applications

The findings from this study suggest that *H. pylori* eradication therapy may be an initial treatment option for localized *H. pylori*-negative gastric MALT lymphoma. Their study adds information which helps in the establishment of strategies for patients with localized *H. pylori*-negative gastric MALT lymphoma.

Peer review

This is an interesting paper that may be beneficial for patients with *H.pylori*-negative gastric MALT lymphoma.

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