

• *H pylori* •

Low grade gastric mucosa associated lymphoid tissue lymphoma: Treatment strategies based on 10 year follow-up

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Abstract

AIM: To deduce strategic guidelines of gastric mucosa associated lymphoid tissue lymphoma (MALTOMA) by evaluating the long-term outcome of patients in respect to various treatment modalities.

METHODS: A total of 55 patients with MALTOMA from May 1992 to August 2002 were retrospectively reviewed.

RESULTS: Complete remission was obtained in 24 (82.8%) of 29 patients treated with anti *Helicobacter pylori* (*H pylori*) regimen only. The duration to reach complete remission was 12 months (85 percentile, 2-33 months). Five patients showed complete remission with radiation therapy (26-86 months). Two of them were *H pylori* treatment failure cases.

CONCLUSION: *H pylori* eradication is an effective primary treatment option for low grade MALTOMA and radiation therapy could be considered in patients with no evidence of *H pylori* infection or who do not respond to *H pylori* eradication therapy 12 months after successful eradication.

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INTRODUCTION

In 1983, Isaacson and Wright introduced the term mucosa associated lymphoid tissue lymphoma (MALTOMA) to characterize primary low grade gastric B-cell lymphoma and immunoproliferative small-intestinal disease^[1]. Subsequently, the definition of MALTOMA was extended to include several other extranodal low grade B-cell lymphomas, with a similar histology to Payer's patches, including those of the salivary gland, lung, and thyroid, but gastric form is the most common and best characterized MALTOMA^[2].

Low grade MALTOMA is composed of small cells with dense nuclear chromatin and a low proliferation fraction, the converse is true for diffuse large B cell lymphoma. Low grade gastric MALTOMA is a neoplasia with a very indolent course and an excellent prognosis. It has a tendency to remain localized to the gastric wall and seldom involves lymph nodes and bone marrow.

In the past, primary low grade gastric MALTOMA was treated with surgery in the same way as adenocarcinoma. This often necessitated a total gastrectomy due to the multi-focal or diffuse nature of gastric lymphomas. Since the introduction of *H pylori* concept, the association of this bacterium with chronic active gastritis, peptic ulcer and gastric cancer has been demonstrated^[3-5]. Furthermore, *H pylori* is suggested to be associated with low-grade gastric MALTOMA. It was proposed that low grade gastric MALTOMA be formed by the immune response to *H pylori* infection in the gastric mucosa^[6,7]. The discovery of a causal role for *H pylori* in the development of gastric marginal zone lymphoma of the MALT type has dramatically altered the therapeutic approach to patients with early stage disease^[8,9]. According to recent data, durable complete remissions might be achieved in up to 80% of patients with early stage MALTOMA following eradication of the bacteria^[9]. In patients who failed to respond to *H pylori* eradication or had low grade gastric MALTOMA without *H pylori* infection, radiotherapy, chemotherapy or surgery has been tried.

However, the long-term follow-up result of *H pylori* eradication on low grade MALT lymphoma has been seldom reported. Furthermore, a clear-cut time is difficult to define the failure to *H pylori* eradication therapy and currently there has been no standard guidelines to assess the result of eradication therapy. Also the time interval to perform endoscopic examination to evaluate histologic and morphologic remission is unclear. Consequently, a suitable strategic guideline to decide subsequent treatment option when one fails has not been well proposed. We aimed to evaluate the long-term outcome of patients with low grade gastric MALTOMA in respect to various treatment modalities. We also tried to deduce suitable strategic guidelines to treat low grade gastric MALTOMA.

MATERIALS AND METHODS

Patients

We retrospectively studied 55 patients with primary low grade gastric MALTOMA aged 23 to 74 years from May 1992 to August 2002. All the patients were pathologically confirmed as low grade gastric MALTOMA. The diagnosis of low grade gastric MALTOMA was made according to the criteria of Isaacson^[10] and scoring system of Wotherspoon *et al*^[11]. The initial staging procedures included a complete physical examination, chest roentgenogram, bone marrow examination, abdominal CT scan and endoscopic ultrasonography (EUS).

Methods

We evaluated the patients' initial presenting symptoms and the status of *H pylori* infection. *H pylori* infection was diagnosed by rapid urease test (CLOTM, Delta West, Bentley,

Western Austria), and/or histologic examination. *H pylori* status was considered to be positive if any of the two tests was positive. Endoscopic findings included the shape, size, location and number of lesions. Gross phenotype was classified according to the endoscopic features into seven types: 1) gastritis: only mucosal color change, 2) granular: small nodules on the lesion, 3) ulcerative: one or more ulcerations, 4) ulceroinfiltrative: one or more ulcerations with surrounding mucosal infiltration, 5) depressed: depressed or EGC IIc like lesion, 6) protruding: elevated or polypoid, and 7) mixed, and then was categorized into diffuse and localized type according to the pattern of distribution.

RESULTS

Clinical and endoscopic features of patients

The male to female ratio was 1:1.3. The mean age of the patients was 47.8 years (23-74). All but three of the patients were symptomatic at presentation. The main symptoms were abdominal pain (56.4%), indigestion (23.6%), epigastric discomfort (12.7%) and vomiting (1%). A total of 48 (48/53, 90.5%) met the case definition for *H pylori* positivity (Table 1). When each test was considered individually, *H pylori* infection was detected by histology and rapid urease test in 42 (87.5%) and 39 (81.3%) patients, respectively. Initial endoscopic findings are summarized in Table 2.

Table 1 Clinical features of patients and *H pylori* state (n=55)

Age (years)	47.8±11.3 (23-74)	
Sex	Male:Female=24:31	
<i>H pylori</i> status ^a	Positive	48 (90.5%)
	Negative	5 (9.5%)

^aExcluding two cases of unknown *H pylori* status.

Table 2 Endoscopic findings and location of low grade MALTOMA (n=55)

Location	No. of cases (%)	Findings	No. of cases (%)
Body only	21 (38.2)	Ulcerative	15 (27.3)
Antrum only	11 (20.0)	Mixed	15 (27.3)
Antrum & body	20 (36.4)	Ulceroinfiltrative	10 (18.2)
Fundus/Cardia	3 (5.4)	Depressed	6 (10.9)
		Gastritis	5 (9.1)
		Protruding	3 (5.5)
		Granular	1 (1.8)

Treatment modalities and outcomes

Treatment modalities included *H pylori* eradication, surgery, radiotherapy and combination therapy (Table 3). A total of twenty nine patients were treated with *H pylori* eradication therapy (omeprazole + amoxicillin + metronidazole or clarithromycin for 2 weeks). All but one was positive in urease test or histologic examination for *H pylori*. Endoscopic ultrasonography was done before *H pylori* eradication and cases with lymph node metastasis or involvement beyond the submucosal layer were excluded. For determination of the response, two months after the end of eradication therapy, biopsy specimens were collected from the multiple sites including the lesion for histologic examination. One additional specimen was obtained for rapid urease test. For the remission failure case, a repeat endoscopy was performed every two to three months until complete remission was achieved. In cases with complete remission, endoscopic examination and biopsy were performed every 6-12 months. Overall *H pylori* eradication rate was 96.4% (27/28). Complete remission of

low grade MALTOMA was achieved in 24 out of 29 cases (82.8%). The median time to get complete remission was 4 months (2-33) (Table 3). In terms of histologic remission of the low grade gastric MALTOMA, the mucosal lesions changed to atrophic or endoscopically normal appearance (Figure 1). There were five treatment failures to *H pylori* eradication therapy. Radiation treatment was given in two patients who failed to respond to anti *H pylori* treatment after 6 months and 9 months of follow-up, respectively. One underwent operation. They all had complete remission in the subsequent follow-up. The remaining two patients were recommended to receive other treatment with persistence of localized MALTOMA.



Figure 1 A: A case with irregular ulceration on the anterior wall of antrum before eradication. B: Three months after *H pylori* eradication therapy, ulceration was disappeared. C: A case with mucosal nodularities on the posterior wall of the upper body before eradication. D: Two months after *H pylori* eradication therapy, the lesion was replaced by atrophic mucosa.

Sixteen patients underwent surgery, including 11 total gastrectomies and 5 subtotal gastrectomies (Table 3). Most of them were treated by surgery because they were suspected to have lymph node metastasis or infiltration beyond the submucosal layer in endoscopic ultrasonographic examination. Among the sixteen patients, 4 patients showed lymph node metastasis. Three patients received additional radiation therapy or chemotherapy after surgery because of lymph node metastasis or perigastric fat infiltration of low grade gastric MALTOMA.

Five patients received radiation therapy. These cases included two patients with *H pylori* negativity, two patients with failure to *H pylori* eradication, and one case with recurrence in remnant stomach after surgery (Table 3). The median radiation dose was 30.6 Gy (range 30-39) with a daily fraction of 1.5-1.8 Gy.

The comparative study among different endoscopic types of low grade MALT lymphoma patients who showed failure to eradication treatment disclosed no significant correlation. However, the lesion of localized mass type showed the tendency to higher treatment failure (Table 4).

Table 3 Initial treatments and outcomes of low grade MALTOMA

	<i>H pylori</i> eradication (n=29)	Surgery (n=16)	Radiotherapy (n=5)
Complete remission (%)	24 (82.8%)	16 (100%)	5 (100%)
Failure (%)	5 (17.2%)	0	0
Recurrence (%)	1 (4.2%)	1	0
Median follow-up (months)	24 (2-74)	46.5 (12-120)	35.5 (26-86)
Time to get CR in 85 percentile of patients (interval) (months)	12 (2-33)		

CR: Complete remission.

Table 4 Failures of *H pylori* eradication treatment according to endoscopic findings

Endoscopic types	Treatment cases	Failure cases (%) ^a
Diffuse	13	1 (17.7) ^b
Gastritis	2	0 (0)
Granular	1	0 (0)
Mixed	10	1 (10.0)
Localized	16	4 (25.0) ^a
Ulcerative	8	2 (25.0)
Ulceroinfiltrative	3	1 (33.3)
Depressed	4	0 (0)
Protruding	1	1 (100.0)
Total	29	5 (17.2)

^aFailure rate of each endoscopic type, ^b $P > 0.05$ by χ^2 test.

DISCUSSION

The relationship between *H pylori* and low grade gastric MALTOMA is strong, and therefore treatment strategies are aimed at *H pylori* eradication in early stages. Recently, durable complete remissions have been supposed to achieve in up to 80% of patients with early stage MALTOMA following eradication of the bacteria^[9]. In the largest MALTOMA study to date, 120 patients with early stage low grade gastric MALTOMA were treated with *H pylori* eradication therapy and followed^[12]. After a mean follow-up period of 48 months, 81% of patients had complete remission. Relapse after complete remission occurred in less than 10% of cases, and whether this was always caused by *H pylori* reinfection has been unknown^[13-24]. Follow-up is essential in patients with

MALTOMA treated with *H pylori* eradication therapy. Endoscopic follow-up with biopsy for histology and *H pylori*, and EUS at least yearly after remission was recommended^[12,25]. Because some residual cells lay dormant after clinical and histological remission was achieved, some investigators insisted that molecular studies should be included in addition to histologic study^[20]. At present, histologic study is considered as the gold standard.

Because eradication therapy is never 100% successful, it is also important to choose the most suitable additional treatment for treatment failure. MALTOMA that was not *H pylori* positive or did not respond to eradication therapy could be treated with surgery, radiation, or chemotherapy. Radical gastrectomy has 5- and 10-yr survival rates of 90% and 70%, but leads to significant morbidity^[26]. Monotherapy with alkylating agents was tried in MALTOMA patients who did not respond to *H pylori* eradication therapy. In this study, remission could be achieved with chlorambucil in only 58% of the nonresponding patients to *H pylori* eradication therapy^[25].

Our results showed 82.8% of remission induction in low grade gastric MALTOMA by *H pylori* eradication alone with a single relapse. About 50% of patients with low grade gastric MALTOMA showed complete remission by 4 months after *H pylori* eradication. However, delayed response by up to 33 months occurred in one case. Overall, complete remission was achieved within 12 months in 85 percentile. We propose that it is necessary to wait for 12 months after initial eradication therapy of *H pylori* to define the time for *H pylori* eradication failure, because relapse is relatively rare after 12 months and nearby all the cases would have complete remission by 12 months. In addition, other treatment modalities could be used 12 months after initial *H pylori* eradication therapy, such as radiation therapy, surgery or chemotherapy.

A recent series from the memorial Sloan-Kettering Cancer Center and Yonsei Cancer Center reported a 100% complete remission rate with radiation alone. Especially, radiation therapy was chosen in the management of low grade gastric MALTOMA in patients with no evidence of *H pylori* infection or who showed no response to *H pylori* eradication therapy^[27,28]. In our study, complete remission was obtained in all the patients after various treatment modalities. All the patients who received radiotherapy tolerated the treatment well and completed the treatment course without significantly acute or delayed toxicities. Radiation therapy was superior to surgery or chemotherapy because it had significant advantages of gastric preservation and lower morbidity.

Our results provide further supports to the recommendation by Issacson and Spencer that eradication of *H pylori* is harmless and inexpensive and should be the first-line treatment for localized low grade gastric MALTOMA. If no response is observed by 12 months after eradication therapy, radiotherapy should be considered.

Several investigators evaluated endoscopic appearance of primary gastric lymphoma^[29,30]. In low grade lymphoma, endoscopic findings were often interpreted as a benign condition, in contrast to high grade lymphoma, for which carcinoma was the most frequently suspected diagnosis. Our results were consistent with previous reports that low grade gastric MALTOMA was found at a relatively high frequency (94.6%) in the middle third of the stomach^[31]. The most frequent endoscopic appearance of gastric lymphoma was ulceration, while the finding of polypoid lesions or other forms (as gastritis or erosions) had a lower frequency^[32]. Also in this study, the majority of the endoscopic features of low grade gastric MALTOMA was superficial, such as shallow ulceration or mixed type, and was multiple rather than single. But these cases also exhibited varied pictures. In terms of the result of *H pylori* eradication therapy, we did not see any correlation

with the endoscopic findings. It might be due to the small number of cases of *H pylori* eradication failure and complexity of endoscopic findings of low grade MALTOMA. However, the lesion of localized mass type showed the tendency to higher treatment failure (Table 4). Nevertheless, if we consider the fact that high grade lymphoma is often accompanied by deep ulceration or protruding mass in the stomach, our results might be valuable on the presumption that mixed type MALTOMA might exist which is responsible for the treatment failure.

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