Is narrow-band imaging useful for histological evaluation of gastric mucosa-associated lymphoid tissue lymphoma after treatment?

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Background and Aim: Endoscopic diagnosis of stomach mucosa-associated lymphoid tissue (MALT) lymphoma is often difficult because few specific findings are indicated. Even when MALT lymphoma is suspected by endoscopy, it is still difficult to make a definitive diagnosis by biopsy because lymphoma cells sometimes distribute unevenly. We previously reported that a tree-like appearance (TLA) is a characteristic finding of MALT lymphoma by narrow-band imaging (NBI) magnifying endoscopy and it is valuable in the selection of an optimal biopsy site in MALT lymphoma. Here, we study the frequency of TLA and evaluate the relationship between the response to eradication therapy and TLA in MALT lymphoma.

Methods: We retrospectively examined the clinical background, endoscopic findings, response to eradication therapy, and Helicobacter pylori infection status of 16 patients diagnosed with MALT lymphoma who were referred to our hospital from April 2007 to August 2012. The regimen for eradication therapy consisted of rabeprazole, with amoxicillin and clarithromycin, all given for 7 days.

Results: TLA was found in 75% (12/16) and H. pylori infection in 75% (12/16) of patients diagnosed with MALT lymphoma by NBI magnifying endoscopy. In all complete regression (CR) patients after eradication treatment, the TLA finding had disappeared (100%); however, in the non-CR patients, TLA remained the same as before the eradication therapy (P = 0.002).

Conclusion: These results suggest that NBI magnifying endoscopy may be useful not only in the diagnosis but also in the evaluation of the response to eradication therapy of MALT lymphoma of the stomach.

Key words: eradication, Helicobacter pylori, mucosa-associated lymphoid tissue (MALT), narrow-band imaging (NBI)

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma is a low-malignancy lymphoma arising from marginal zone B-cells caused by chronic infection that can develop in extranodal organs such as the gastrointestinal (GI) tract, thyroid gland, and lungs out of a knob backed by chronic inflammation. This entity was first described and established in 1983 by Isaacson and Wright.1 Most MALT lymphomas are believed to be caused by chronic gastritis as a result of Helicobacter pylori infection. H. pylori provides an antigenic stimulus that activates mucosal T cells, a phenomenon that is necessary for sustaining the growth and progression of gastric MALT lymphoma. It has already been reported that 60–80% of patients respond to H. pylori eradication treatment,2,3 and eradication therapy has become widely accepted as an initial treatment. Gastric MALT lymphoma is often misdiagnosed as early cancer and gastritis by endoscopic diagnosis because of the various macroscopic patterns. Even when MALT lymphoma is suspected, it is sometimes difficult to make a definitive diagnosis, even after biopsy. We previously reported that a tree-like appearance (TLA) is a characteristic finding of MALT lymphoma by narrow-band imaging (NBI) magnifying endoscopy4 and it is valuable in the selection of an optimal biopsy site in MALT lymphoma.5

However, from our experience, TLA is absent in some cases of gastric MALT lymphoma and, importantly, the
The prevalence of TLA in MALT lymphoma has not been investigated. In this study, we retrospectively investigated the prevalence of TLA in gastric MALT lymphoma patients and the usefulness of NBI done before and after therapy to judge the effect of eradication therapy on cases with TLA.

**METHODS**

We retrospectively examined all 16 patients who were diagnosed with gastric MALT lymphoma and who were referred to our hospital from April 2007, when our hospital opened, to July 2011. All cases were examined by upper GI endoscopy. We studied the clinical background, endoscopic findings, NBI findings, endoscopic ultrasonography (EUS) findings, efficacy of eradication therapy, and *H. pylori* infection status of these 16 patients (Table 1). We followed the World Health Organization (WHO) classification for the diagnosis of MALT lymphoma. Staging was done using the Lugano Staging System based on upper GI tract endoscopy, lower GI tract endoscopy, and whole-body computed tomography (CT) examination. Macroscopic type was classified into three groups: early-stage gastric carcinoma-like pattern, gastritis-like pattern, and submucosal tumor-like pattern, as previously described.

GIF-Q240Z (Olympus, Tokyo, Japan) was used for the NBI examination. In cases in which MALT lymphoma was observed, we defined TLA on images with abnormal blood vessels resembling branches from the trunk of a tree in which the glandular structure was lost (Fig. 2). In magnified NBI, the inside of the whole stomach was closely observed for some time, with centering of lesions, at weak to intermediate magnification after conventional observation. The lesions were judged as TLA-positive when the features defined above were noted and TLA-negative when no features were noted. Lesions were judged by two endoscopists familiar with NBI. The course after eradication was followed by endoscopy (including NBI) and biopsy every 2–3 months.

Diagnostic testing for *H. pylori* infection was done by tissue examination of endoscopic biopsy specimens and immunoglobulin (Ig)G antibody titer examination against *H. pylori*, or histological examination and the urea breath test. The patient was judged as ‘infected’ when any tests were positive and ‘not infected’ when all tests were negative. Response to eradication therapy for *H. pylori* was evaluated by urea breath test 4–6 weeks after eradication.

The regimen for eradication therapy consisted of sodium rabeprazole 10 mg/day, with amoxicillin hydrate (AMPC) 750 mg twice a day and clarithromycin (CAM) 400 mg twice a day, all given for 7 days. Radiotherapy (30 Gy irradiation to the whole stomach) was carried out as a second-line therapy when there was no improvement or progressive disease after 1 year with eradication therapy.

Assessment of responsiveness was done according to the Bayerdorffer classification as complete regression (CR), partial regression (PR), or no change (NC). Finally, PR and NC cases were classified as non-CR cases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Background and clinical features of patients and tumors (n = 16)</th>
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<tr>
<td></td>
<td>TLA-positive patients (n = 12)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>7</td>
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<td>Female</td>
<td>5</td>
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<tr>
<td>Age (mean years)</td>
<td>62 (range 37–79)</td>
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<td>Stage</td>
<td>12</td>
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<td>Endoscopic phenotype</td>
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<td>G-like pattern</td>
<td>6</td>
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<td>EGC-like pattern</td>
<td>5</td>
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<tr>
<td>SMT-like pattern</td>
<td>1</td>
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<td>Depth (EUS)</td>
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<td>M</td>
<td>3</td>
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<td>SM</td>
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<td>MP</td>
<td>0</td>
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<tr>
<td>Unknown</td>
<td>8</td>
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<tr>
<td>H. pylori infection</td>
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<td>Positive</td>
<td>8</td>
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<td>Negative</td>
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EGC-like pattern, early gastric cancer-like pattern; EUS, endoscopic ultrasonography; G-like pattern, gastritis-like pattern; SMT-like pattern, submucosal tumor-like pattern; TLA, tree-like appearance.
CR was evaluated if complete disappearance of the lesion was observed by normal endoscopy (Fig. 2a,b). Moreover, the cases with TLA by NBI examination were evaluated pathologically by biopsy of the lesion. Several areas with TLA were biopsied because residual MALT lymphoma was suspected, even upon disappearance of the lesion by normal observation.

**Statistical analysis**

The CR rate to eradication therapy between the patients whose TLA disappeared and those whose TLA remained was compared with Fisher’s exact probability test; *P*-value <0.05 was considered to indicate statistical significance.
RESULTS
Clinical background
We retrospectively examined 16 patients diagnosed with gastric MALT lymphoma, 10 male and six female patients, aged between 22 to 79 years, with an average age of 60.1 years. The clinical stage of all 16 patients was stage I by the Lugano Staging System (Table 1).

Endoscopic images
Although various macroscopic patterns such as multiple erosions, cobblestone-like appearance, and ulcerations resembling early cancer were observed, three main patterns were recognized: (i) gastritis-like pattern \( n = 7 \); (ii) early gastric cancer-like pattern \( n = 7 \); and (iii) submucosal tumor-like pattern \( n = 2 \). TLA were recognized in 75\% (12/16) of patients by NBI magnifying endoscopy.

For the six patients examined by EUS, four cases were suspected of having a mucosal lesion (M) and two of these four cases achieved CR after eradication therapy. One case in PR with suspected submucosal infiltration (SM) achieved CR after irradiation therapy. One case in NC with suspected infiltration into the muscular layers achieved CR after irradiation therapy.

Response to H. pylori infection and eradication therapy
Responses to MALT lymphoma after H. pylori infection and eradication therapy are shown in Figure 3 and Table 2. Twelve cases (75\%) were recognized as having H. pylori infection (Table 1). In the present study, all 16 cases underwent eradication therapy for initial treatment regardless of the presence or absence of H. pylori infection. We judged that successful H. pylori eradication was carried out in 12 H. pylori-positive cases because urea breath tests became negative. However, 3/12 cases (25\%) did not achieve CR by endoscopic and pathological evaluations after 1 year with eradication therapy, and underwent radiation therapy. Three cases achieved CR with radiation therapy. Three cases in non-CR after eradication therapy that were negative for H. pylori infection achieved CR with radiation therapy. One out of four cases negative for H. pylori infection demonstrated an effect of eradication therapy, and the MALT lymphoma achieved CR from endoscopic and pathological evaluations.
Table 2 shows the relationship between the histological findings of biopsy specimens and the disappearance of TLA in 12 patients in whom TLA was noted before eradication therapy. TLA disappeared in all eight patients in whom no residual MALT lymphoma was observed on biopsy after therapy (Fig. 2c,d), whereas TLA remained in all four patients in whom residual MALT lymphoma was noted on biopsy ($P = 0.002$), showing that the sensitivity and specificity were 100%.

DISCUSSION

GASTRIC MALT LYMPHOMA is often misdiagnosed endoscopically as gastric ulcer, gastritis, or gastric cancer because the endoscopic features of gastric MALT lymphoma are variable. It is important to suspect gastric MALT lymphoma initially because of the various macroscopic patterns, even when multiple biopsies cannot produce a definitive diagnosis of MALT lymphoma.

It is reported that 10–20% of cases by initial endoscopy and 50–70% of cases by biopsy were diagnosed as MALT lymphoma. One of the reasons for misdiagnosis might be the low incidence of stomach MALT lymphoma; that is, 1–7% within gastric malignant disease.

We defined TLA on the images of abnormal blood vessels resembling from the trunk of a tree, in which the glandular structure was lost, by NBI observation. Ono et al. defined abnormal blood vessels in MALT lymphoma as blood vessels irregular in size and formation, and seen in normal mucosa; however, this definition lacks objectivity, and differentiation from blood vessels in the surrounding gastric mucosa is difficult. Tree branch-like abnormal blood vessels defined as per our definition can be readily identified, and the presence of similar blood vessels has recently been reported by Norimura et al. We reported the usefulness of targeted biopsy under NBI endoscopy for the improvement of diagnostic accuracy. Biopsy is the gold standard for the diagnosis and evaluation of gastric MALT lymphoma, and endoscopists must carry out a target biopsy for correct pathological diagnosis.

Tree branch-like abnormal blood vessels observed in MALT lymphoma are useful for differentiation from undifferentiated-type early gastric cancer, which is difficult by conventional observation. Glandular structures also disappear in undifferentiated-type early gastric cancer on magnified NBI, similar to those in MALT lymphoma, but abnormal blood vessels are curly and variable in diameter, which can be readily differentiated from tree branch-like abnormal blood vessels in MALT lymphoma. Bifurcation with tapering like a tree branch is observed in abnormal blood vessels with TLA.

Isomoto et al. reported the destruction and loss of glandular structures as magnified chromoendoscopic findings of MALT lymphoma, but they did not mention the presence of abnormal blood vessels. Ono et al. reported that non-structural areas and abnormal vessels were observed before treatment in all gastric MALT lymphoma patients. However, from our experience, non-structural areas and abnormal vessels defined as TLA by us are absent in some cases of gastric MALT lymphoma, and it is necessary to analyze the frequency of TLA because gastric MALT lymphoma without TLA does exist. As mentioned earlier, it would take a long time to examine many cases of gastric MALT lymphoma and it is difficult to collect cases that have undergone upper GI endoscopy, including NBI, because gastric MALT lymphoma is a rare malignancy.

In our hospital, all patients who underwent upper GI endoscopy also underwent NBI. Although the number of cases was small at 16, we could retrospectively review all patients with a diagnosis of gastric MALT lymphoma in previous hospitals who were referred to our hospital. The rate of TLA was 75% of the cases; however, the rate of diagnosis of gastric MALT lymphoma by initial endoscopic examination under white light was 10–20%. Therefore, it is suggested that TLA by NBI could be a useful marker for better diagnostic efficacy. It has already been reported that lymphoma cells migrate into the lamina propria mucosae and ischemia leads to vascular endothelial growth factor (VEGF) activity. Neovascularization induced by VEGF might be related to the TLA feature. Therefore, a target biopsy may contribute to an inaccurate diagnosis. Nakamura et al. reported the predictive value of endoscopic ultrasonography for regression of gastric MALT lymphomas. They found that 93% of MALT lymphomas restricted to the mucosa but only 23% of lymphomas that had invaded the deep portion of the submucosa or beyond completely regressed; they thus concluded that the assessment of deep submucosal invasion by endosonography is valuable for predicting the efficacy of $H. pylori$ eradication in gastric MALT lymphoma. As EUS was used in only six out of 16 cases in this study, it is difficult to evaluate. Two of four (50%) cases with M by EUS achieved CR after eradication therapy, and one case with SM and one case with MP achieved non-CR after eradication therapy. In the present study, all 16 cases underwent eradication therapy as initial treatment regardless of the presence or absence of $H. pylori$ infection. All 12 $H. pylori$-positive cases were successfully eradicated.

Nine out of 12 cases with $H. pylori$ positivity achieved CR and one of four cases with $H. pylori$ negativity achieved CR. The CR rate was 62.5%. It was reported that 60–90% of gastric MALT lymphoma patients were infected by $H. pylori$ in the stomach mucosa. The rate of response to eradication...
was reported to be 60–80%. Therefore, our results are the same as in previous reports. One of four (25%) patients with H. pylori-negative gastric MALT lymphoma achieved CR by eradication therapy. Asano et al. also reported that H. pylori eradication therapy achieved a CR rate of 29.4% in patients with H. pylori-negative gastric MALT lymphoma. These results suggest the possibility that microorganisms other than H. pylori are involved in the development of MALT lymphomas and eradicated, but further studies are warranted. No marked difference was noted in the background between TLA-positive and -negative patients, as shown in Table 1, but the number of cases was very small. Further accumulation of cases and investigation may be necessary. Currently, we select radiotherapy as a second-line therapy when CR is not achieved 1 year after eradication. The time required to reach CR of gastric MALT lymphoma varies from 1 month to more than 1 year among CR cases. Yamashita et al. reported that whether or not CR will be achieved can be predicted by biopsy 1–2 months after eradication. It was stated in another report that continuation of course observation without treatment; namely, ‘watch and wait’, for 2 years after eradication is desirable. We are planning to investigate the timing of introducing a second-line therapy.

As shown in Table 2, a correlation was noted between residual MALT lymphoma after treatment and the disappearance or retention of TLA in cases with TLA before treatment, and the sensitivity and specificity were 100%. These results suggest that NBI examination is very useful in judging the effectiveness of eradication of TLA-positive cases. In the present study, the number of cases was small, but the results suggest that NBI magnifying endoscopy is useful not only in the diagnosis but also in the evaluation of the response to eradication therapy of MALT lymphoma of the stomach. Nowadays, the number of elderly people taking an anticoagulant is increasing. If the characteristic finding, TLA, is observed in gastric MALT lymphoma at a high frequency, as in the present study (75%), and treatment is successful and results in the disappearance of both MALT lymphoma and TLA, the combination of NBI, instead of biopsy, with conventional endoscopy and histological examination every 2–3 months after treatment may decrease the frequency of biopsy. However, the number of cases in this study was small, and further accumulation of cases and investigation are necessary. In addition, further investigation of the differences between TLA-positive and -negative patients may also be necessary.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

REFERENCES


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