Prospective Study of Helicobacter pylori Eradication Therapy in Stage I E High-Grade Mucosa-Associated Lymphoid Tissue Lymphoma of the Stomach

By Li-Tzong Chen, Jaw-Town Lin, Rong-Yaun Shyu, Chang-Ming Jan, Chi-Long Chen, I-Ping Chiang, Shiang-Ming Liu, Ih-Jen Su, and Ann-Lii Cheng

Purpose: High-grade mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach are generally believed to be Helicobacter pylori-independent, autonomously growing tumors. However, anecdotal cases of regression of high-grade lymphomas after the cure of H pylori infection had been described. The present prospective study was conducted to evaluate the effect of anti-H pylori therapy in stage I E high-grade gastric MALT lymphomas.

Patients and Methods: Sixteen patients with H pylori infection and stage I E gastric high-grade MALT lymphoma consented to a brief antibiotic therapy as first-line treatment from June 1995 through April 2000. Then, patients underwent intensive endoscopic follow-up examinations (endoscopic ultrasonography) with biopsy to evaluate tumor response. Patients with significant improvement of gross lesions that accompanied regression of large cells were followed up without additional treatment. Patients without significant improvement were immediately referred to systemic chemotherapy.

Results: Eradication of H pylori was achieved in 15 patients and was accompanied by rapid gross tumor regression and disappearance of large cells in 10. All 10 of these patients with early response had subsequent complete histologic remission of lymphoma. The complete remission rate was 62.5% (95% confidence interval, 35.8% to 89.1%). The response rate was not affected by the tumor grading (proportion of large blast cells within the tumor) but was adversely affected by the depth of tumor invasion. At a median follow-up of 43.5 months (range, 21.1 to 67.4 months), all 10 of these patients remained lymphoma-free. The median duration of complete response was 31.2 months (range, 14.4 to 49.1 months).

Conclusion: These results suggest that high-grade transformation is not necessarily associated with the loss of H pylori dependence in early-stage MALT lymphomas of the stomach.

aggressive lymphomas, the Clinical Advisory Committee of the World Health Organization has recommended that the term diffuse large B-cell lymphomas with areas of marginal zone/MALT lymphoma be used to describe these tumors rather than high-grade MALT lymphoma.21 This study investigated the efficacy of anti-\textit{H pylori} therapy as first-line treatment for stage I\textsubscript{g} high-grade gastric MALT lymphomas. The histologic criteria for high-grade transformation used in this study is the presence of compact confluent clusters or sheets of large cells in MALT lymphomas, as proposed by Chan et al.23 This is the first prospective study to demonstrate the effectiveness of \textit{H pylori} eradication in the treatment of early-stage high-grade MALT lymphoma of the stomach. These results suggest that the therapeutic approach for primary high-grade gastric MALT lymphoma should involve \textit{H pylori} eradication in the first line of treatment.

**PATIENTS AND METHODS**

From June 1995 through April 2000, patients with stage I\textsubscript{g} high-grade gastric MALT lymphoma and \textit{H pylori} infection who were diagnosed by or referred to our clinics in four medical centers in Taiwan were recruited for participation in this study. All the endoscopic biopsy specimens were independently reviewed by the reference hematopathologist, I.-J.S., and by at least two of three additional experienced hematopathologists (C.-L.C., I.-P.C., and S.-M.L.). The diagnostic criteria of high-grade MALT lymphoma was in accordance with the proposal of Chan et al.23 and was defined as the presence of confluent clusters or sheets of large cells resembling centroblasts or lymphoblasts within predominantly low-grade centrocyte-like cell infiltrate, or a predominance of high-grade lymphoma with only small, residual, low-grade foci and/or the presence of lymphoepithelial lesions.18,19,22 If only a few scattered transformed blast cells or sheets of transformed blast cells confined within the colonized follicles were found within a low-grade lymphoma, they were considered as an immune response to \textit{H pylori} stimulation rather than high-grade MALT lymphoma.16–19 Patients with primary pure large-cell lymphomas, without evidence of a low-grade component, of the stomach were excluded.

Staging work-up included detailed physical examination, inspection of Waldeyer’s ring, computed tomography of the chest and abdomen, small-bowel series, barium enema study of the colon and rectum, and bone marrow aspiration and biopsy.26 Classification of the tumor as stage I\textsubscript{g} of the Musshoff’s modification of the Ann Arbor staging system indicated that the tumor was limited to the stomach.27 Patients who were treated and followed up at National Taiwan University Hospital also had endoscopic ultrasonography (EUS) with an Olympus transendoscopic miniature ultrasonic probe UM-2R or UM-3R (Olympus Optical Co Ltd, Tokyo, Japan), to evaluate the depth of tumor infiltration and the status of perigastric lymph nodes and to guide tissue sampling.

All patients consented to a brief trial of \textit{H pylori} eradication therapy. At the beginning of the study, the eradication regimens consisted of amoxicillin 500 mg and metronidazole 250 mg qid with either bismuth subcitrate 120 mg qid or omeprazole 20 mg bid for 4 weeks, which was changed to amoxicillin 500 mg qid, clarithromycin 500 mg bid, plus omeprazole 20 mg bid for 2 weeks after March 1996. Patients were scheduled for first follow-up upper gastrointestinal endoscopic examination 4 to 6 weeks after completion of antimicrobial therapy, and follow-up was then repeated every 6 to 12 weeks until histologic evidence of remission was obtained. On each occasion, four to six biopsy specimens were taken from the antrum and body of the stomach for the evaluation of \textit{H pylori} infection, and a minimum of six biopsy specimens were taken from each of the tumors and suspicious areas for histologic evaluation. \textit{H pylori} infection was determined by histologic examination, biopsy urease test, and bacterial culture. Histologic features were evaluated using the scoring system described by Wotherspoon et al.4 The proportion and distribution of large cells were evaluated in detail. Complete histologic remission was defined as a Wotherspoon’s score of 2 or less on every histologic section of the biopsy specimens. In patients with complete histologic remission of tumors, endoscopic examination of the stomach and computed tomography of the abdomen were repeated every 3 to 6 months. In patients with grossly stable or progressive disease on follow-up endoscopic examination and in patients with a persistent or increasing proportion of large cells on microscopic examination, systemic chemotherapy with cyclophosphamide, doxorubicin, and vincristine with or without prednisolone was given.28,29

The association between discrete variables was assessed using Fisher’s exact test. A value of \( P < .05 \) was considered statistically significant.

**RESULTS**

**Clinicopathologic Features of the Patients**

Six men and 10 women with a median age of 55.0 years were enrolled onto the study. The clinical presentation of these patients included epigastric pain of a variable duration in 12, hematemesis in two, and incidental discovery of tumor during a general health check-up in two (Table 1). One patient who presented with hematemesis had undergone emergency laparotomy with wedge resection of a bleeding gastric tumor. Follow-up endoscopic examination of this patient revealed ulceration at the operation site and biopsy disclosed residual high-grade lymphoma with lymoepithelial lesions on histopathologic examination.

Upper gastrointestinal endoscopic examination revealed ulceration in nine patients (at the angularis in three and at the lower body and/or antrum in six), multiple erosions on nodular infiltrative mucosa in six (at the antrum in one, at the lower body and antrum in three, and at the upper body in two), and multiple erosions on nodular giant folds at the middle and lower body in one. The depth of tumor invasion was evaluated by EUS examination in 10 patients and by histologic examination of the surgical specimen in one patient. The tumor was found to have extended into the submucosa in four patients, the muscularis propria in four, and the serosa in three.

The pretreatment histopathologic features consisted of either apparent foci of clusters or sheets of large blast cells in a background of low-grade MALT lymphoma (nine patients) or frank diffuse high-grade MALT lymphoma with foci of centrocyte-like cells and/or lymphoepithelial lesions (seven patients).
In the present study, eradication of *H pylori* infection resulted in durable long-term complete histologic remission in 10 of 15 patients (66.7%; 95% CI, 39.6% to 93.7%). Complete histologic remission was achieved in five (62.5%) of eight patients with foci of clusters or sheets of large cells in a background of low-grade MALT lymphoma and in five (71.4%) of seven patients with frank diffuse high-grade lymphoma and a diagnostic low-grade component. All four tumors (100%) were limited to the submucosal layers or above, and two (28.6%) of seven tumors that infiltrated into or beyond the muscularis propria responded to anti-*H pylori* therapy (P = .061). The median period between *H pylori* eradication and complete histologic remission was 3.9 months (range, 1.5 to 17.7 months). The changes in the findings of upper gastrointestinal endoscopic and histologic features of a representative case are illustrated in Fig 1. Five patients whose tumors grossly increased in size and showed an increased large-cell fraction microscopically, as well as one patient whose tumor remained grossly stable at first follow-up endoscopic examination, were immediately referred for systemic chemotherapy. All six patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, but only four of them completed six cycles of treatment. The chemotherapy regimen in two elderly patients (73 and 83 years old) who experienced severe myelosuppression and mucositis after their first cycle of CHOP was changed to modified CHOP and oral prednisolone plus chlorambucil, respectively. Five (83.3%) out of the six patients achieved complete remission. One patient who had completed six cycles of CHOP had residual low-grade components with remission of high-grade lymphoma cells.

**Follow-Up**

At a median follow-up of 43.5 months (range, 21.1 to 67.4 months) all 10 patients who achieved complete histologic remission after eradication of *H pylori* were alive and free of lymphoma. The median duration of disease-free survival during the study period was 31.2 months (range, 14.4 to 49.1 months).

**DISCUSSION**

In the present study, eradication of *H pylori* infection resulted in durable long-term complete histologic remission in 10 of 15 patients (66.7%; 95% CI, 39.6% to 93.7%) with stage I<sub>E</sub> high-grade MALT lymphoma of the stomach. This is the first prospective study to demonstrate the effectiveness of *H pylori* eradication in the treatment of early-stage high-grade MALT lymphoma of the stomach. Anecdotal cases of high-grade MALT lymphoma that responded to antibiotic treatment had recently been described by other investigators.\(^\text{30-39}\) An in vitro study by Hussell et al\(^\text{32}\) showed that tumor cells from high-grade gastric MALT lymphoma as well as from low-grade MALT lymphoma of extragastric

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**Table 1. Clinicopathologic Characteristics of 16 Patients With Stage I<sub>E</sub> High-Grade MALT Lymphoma of the Stomach**

<table>
<thead>
<tr>
<th>Clinicopathologic Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21-83</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/10</td>
<td></td>
</tr>
<tr>
<td>Endoscopic feature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple erosion on infiltrative mucosa</td>
<td>6</td>
<td>37.5</td>
</tr>
<tr>
<td>Ulceration or ulcerated mass</td>
<td>9</td>
<td>56.2</td>
</tr>
<tr>
<td>Multiple erosion on nodular giant folds</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Location of tumor(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>7</td>
<td>43.8</td>
</tr>
<tr>
<td>Angularis</td>
<td>4</td>
<td>25.0</td>
</tr>
<tr>
<td>Middle and/or lower body</td>
<td>6</td>
<td>37.5</td>
</tr>
<tr>
<td>Upper body and/or fundus</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Depth of invasion before treatment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submucosa</td>
<td>4/11</td>
<td>36.4</td>
</tr>
<tr>
<td>Muscularis propria</td>
<td>4/11</td>
<td>36.4</td>
</tr>
<tr>
<td>Serosa</td>
<td>3/11</td>
<td>27.2</td>
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<tr>
<td>Initial pathologic feature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade MALT lymphoma with faci of large cell aggregations</td>
<td>9</td>
<td>56.3</td>
</tr>
<tr>
<td>High-grade MALT lymphoma with faci of CCL and/or LEL</td>
<td>7</td>
<td>43.7</td>
</tr>
</tbody>
</table>

Abbreviations: CCL, centrocyte-like cells; LEL, lymphoepithelial lesion.

*Evaluated by EUS in 10 and by histologic examination of surgical specimen in one.
organs did not respond to the costimulation of autologous T cells and lysate of a specific *H pylori* strain, as the low-grade gastric MALT lymphoma cells did. This result is strongly supported by the finding that most cases of antibiotics-resistant low-grade gastric MALT lymphoma contained a high-grade component in the deeper layers of the gastric wall in their gastrectomy specimens.\(^7,8\) High-grade transformation was considered to be responsible for the unfavorable response of these tumors.\(^9\) These data have led to the general belief that high-grade transformation usually arises from *H pylori*-independent, autonomously growing low-grade MALT lymphoma clones, and that high-grade MALT lymphoma is, therefore, unlikely to respond to anti-*H pylori* therapy.\(^22,40,41\) On the basis of these data, only those lymphomas composed mostly of small cells have been included in the category of extranodal marginal zone/MALT-type B-cell lymphoma in the Revised European-American Lymphoma/World Health Organization classification. In contrast, high-grade tumors that have transformed from low-grade MALT lymphomas as well as primary large B-cell lymphomas that occurred in a MALT site are defined as diffuse large B-cell lymphomas (with or without areas of

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**Fig 1.** Complete histologic remission of a high-grade MALT lymphoma to *H pylori* eradication therapy: (A, B) before, (C, D) after 6 weeks, and (E, F) after antibiotic therapy.

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marginal zone/MALT-type lymphoma) to emphasize the antigen-independent and aggressive nature of these tumors and the necessity of aggressive treatment.\(^{21,41}\) However, our results indicate that the emergence of increasing proportion of large cells may not preclude *H pylori* dependence in stage \(I_6\) MALT lymphomas of the stomach.

In this study, tumors that responded to *H pylori* eradication usually showed regression of large cells at the first follow-up examination, and complete histologic remission was achieved in all of these patients within a median period of 3.9 months after *H pylori* eradication. The histologic remission rate of 66.7% and the median time of 3.9 months to complete remission in this study are similar to the results of earlier studies of *H pylori* eradication in low-grade MALT lymphoma.\(^{4,6,13,22,39}\) These findings suggest that high-grade transformation is not necessarily associated with loss of *H pylori* dependence and that the response of large cells to the cure of *H pylori* infection may correspond to the antigen dependency of their low-grade counterpart in stage \(I_6\) high-grade gastric MALT lymphomas.

In this study, the complete histologic remission rate, which was 62.5% in patients with predominantly low-grade tumors and 71.4% in patients with predominantly high-grade tumors, was not affected by the initial histologic grading of the tumors. Recently, de Jong et al\(^{19}\) showed that an increased proportion of large cells in gastric MALT lymphomas adversely affected the complete histologic remission rate and overall survival in gastric MALT lymphoma treated with radiotherapy with or without chemotherapy. They also showed that low-grade gastric MALT lymphomas that contained an increased number of transformed blasts that did not belong to the preexisting germinal center, a finding not diagnostic for overt transformation, were associated with loss of costimulatory markers (notably CD86) on tumor B cells and with inferior response rate (one of eight patients, 12.5%) to *H pylori* eradication therapy.\(^{38}\) The authors proposed that the increment of large cells may not only be a marker of tumor progression toward autonomous growth but is also associated with loss of *H pylori* dependence.\(^{19,38}\) The reason for the discrepancy between our results and those of de Jong et al\(^{19}\) is not clear. Recently, Nakamura et al\(^{39}\) reported a 50% (five of 10 patients) complete response rate in anti-*H pylori* therapy–treated high-grade MALT lymphoma. The 60% (three of five patients) complete response rate in patients who had low-grade MALT lymphoma with a focal high-grade component was similar to the 40% (two of five patients) complete response rate in those who had high-grade MALT lymphoma with a low-grade component. The probability of complete remission at 12 months after *H pylori* eradication was found to correlate only with depth of tumor invasion and not with the presence of a high-grade component.\(^{39}\) These observations strongly support our findings and suggest that the presence of clusters or sheets of large cells may not preclude *H pylori* dependence in early-stage gastric MALT lymphomas.

In our study, the complete histologic remission rate was adversely affected by the depth of tumor invasion, with 100% in tumors limited to the mucosa and submucosa and 28.6% in tumors extending into or beyond the muscularis propria. Despite the limited number of cases in the present study, the difference was borderline significant, \(P = .061\). This finding is similar to the results of Nakamura et al,\(^{39}\) who found that the complete remission rate in high-grade MALT lymphomas restricted to the mucosa/submucosa and in those that invaded into/beyond the muscularis propria was 66.7% (four of six) and 25% (one of four), respectively. These results also concur with those reported by Sackmann et al\(^{42}\) and Ruskone-Fourmestaux et al\(^{13}\) in patients with low-grade MALT lymphoma and suggest that the depth of lymphoma infiltration as determined by EUS is an important prognostic factor of the effect of *H pylori* eradication therapy in stage \(I_6\) high-grade as well as in low-grade gastric MALT lymphoma. These findings suggest that long-term antigen-driven proliferation may cause genetic alternations to occur and to accumulate in *H pylori*–dependent MALT lymphoma cells (both low-grade and high-grade) until *H pylori*–independent autonomously growing clones have evolved. An increase of tumor burden in MALT lymphoma that manifests as bulky tumor, deep infiltration of the gastric wall, or in an advanced stage of disease will be more likely to harbor *H pylori*–independent autonomous clones and be less responsive to antibiotic treatment.\(^{41,43}\)

In this study, most of the tumors that were refractory to antibiotics showed grossly increased size and microscopic evidence of increased large-cell proportion at the first follow-up examination. The rapid progression of gross tumors suggests that the increasing proportion of large cells in follow-up examinations was more likely to result from the autonomous proliferation of large blast cells outgrowing and effacing their antigen-independent, indolent low-grade counterparts rather than from the regression of the antigen-dependent low-grade component within these tumors. Thus, despite a durable complete remission achieved in responding tumors, the potential for rapid tumor growth in antigen-independent, early-stage, high-grade MALT lymphoma should be emphasized. Therefore, initial treatment that involves antibiotic therapy in stage \(I_6\) high-grade gastric MALT lymphoma should be administered only in hospitals, where appropriate histologic grading, radiologic staging,
and an intensive endoscopic follow-up protocol can be strictly executed.

Early initiation of systemic chemotherapy with or without radiotherapy is mandatory when tumors are refractory to antibiotic treatment. The complete remission rate of 83.3% in our patients who had not responded to \textit{H pylori} eradication therapy was compatible with the complete remission rate of 88.2% found in a previous study of a group of patients who received (four patients) and did not receive (13 patients) \textit{anti-}\textit{H pylori} therapy before systemic chemotherapy.\textsuperscript{29} Our findings further justify a brief trial of \textit{H pylori} eradication therapy before systemic chemotherapy in patients with stage I\textsubscript{E} high-grade MALT lymphoma of the stomach when these patients have \textit{H pylori} infection.

Although a larger scale of prospective study is warranted, as suggested by Morgner et al.,\textsuperscript{36} proper staging with EUS, detailed recording of large-cell proportion in histology, and molecular genetic as well as immunologic markers should all be evaluated in such a study.\textsuperscript{39,44} Identification of the molecular and biologic factors associated with the loss of \textit{H pylori} dependence and with high-grade transformation may be of value in tailoring the therapeutic strategy for individual patients with gastric MALT lymphoma.\textsuperscript{45-47}

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\textbf{REFERENCES}


