**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 5127**

**Columns: TOPIC HIGHLIGHTS**

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***Helicobacter pylori* infection in gastric mucosa-associated lymphoid tissue lymphoma**

Park JB *et al.* *H. pylori* and MALT lymphoma

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**Received:** August 16, 2013  **Revised:** October 15, 2013

**Accepted:** November 1, 2013

**Published online:**

**Abstract**

Gastrointestinal lymphoma is the most common type of extranodal lymphoma, and most commonly affects the stomach. Marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphoma are the most common histologic types of gastric lymphoma. Despite its increasing incidence, diagnosis of gastric lymphoma is difficult at an earlier stage due to its nonspecific symptoms and endoscopic findings, and, thus, a high index of suspicion, and multiple, deep, repeated biopsies at abnormally and normally appearing sites in the stomach are needed. In addition, testing for *Helicobacter pylori* (*H. pylori*) infection and endoscopic ultrasonography to determine the depth of tumor invasion and involvement of regional lymph nodes is essential for predicting response to *H. pylori* eradication and for assessment of disease progression. In addition, *Helicobacter pylori* infection and MALT lymphoma development are associated, and complete regression of low-grade MALT lymphomas after *H. pylori* eradication has been demonstrated. Radiotherapy and/or chemotherapy can be used in cases that show poor response to *H. pylori* eradication, negativity for *H. pylori* infection, or high-grade lymphoma.

**Key words:** Mucosa-associated lymphoid tissue; Lymphoma; *Helicobacter pylori*; Eradication; Remission

**Core tip:** The incidence of gastric mucosa-associated lymphoid tissue (MALT) lymphoma is increasing; however, earlier diagnosis is still difficult. Early detection and accurate stage workup is essential for treatment of MALT lymphoma. If gastric lymphoma is verified, testing for *Helicobacter pylori* infection, bone marrow biopsy, chest radiographs, endoscopic ultrasonography, and computed tomography scans should be performed for staging. We reviewed the most recent literature and provide a comprehensive summary of the diagnosis, treatment according to each stage, and follow-up on this topic.

Park JB, Koo JS. *Helicobacter pylori* infection in gastric mucosa-associated lymphoid tissue lymphoma.

**Available from:**

**DOI:**

**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infection, one of the most common chronic infections, has a worldwide distribution. Infection rates differ by country; however, more than half of the world’s population is infected. In addition, *Helicobacter pylori* infection is the primary pathologic cause of development of low-grade, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. International guidelines strongly recommend bacterial eradication in all gastric MALT lymphoma patients[1-4]. In fact, during the early stage low-grade MALT lymphoma can be cured by *H. pylori* eradication in 60%-80% of cases[5-7].

Primary gastrointestinal lymphoma accounts for 30%-40% of all extranodal lymphomas. In addition, the incidence of primary gastric lymphoma has increased in recent decades[8], however, it is still a rare disease. Its lack of specific symptoms and various or nonspecific endoscopic findings make early detection and diagnosis difficult. Therefore, sufficient experience and endoscopic skill are needed in order to determine an accurate pathologic diagnosis and macroscopic lesion range. Here, we provide a review of the characteristics, diagnosis and treatment of primary gastric MALT lymphoma.

**PATHOLOGIC CHARACTERISTICS OF GASTRIC MALT LYMPHOMA**

Based on histologic characteristics, primary gastric lymphomas are classified as diffuse large B-cell lymphoma, marginal zone B-cell lymphoma of the MALT type (MALT lymphoma), follicular lymphoma, mantle cell lymphoma, plasmacytoma, Burkitt’s lymphoma, and T-cell lymphoma. Diffuse large B-cell lymphoma and MALT lymphoma account for approximately 60% and 40% of all gastric lymphomas respectively[9]. MALT lymphoma is defined as a diffuse proliferation of centrocyte-like cells with lymphoepithelial lesions[10], whereas diffuse large B-cell lymphomas are divided into two entities according to the presence or absence of areas of MALT lymphoma[11].

*H. pylori* infection plays an important role in development of almost all MALT lymphomas. Gastric tissue normally does not contain MALT, but may acquire it in response to chronic *H. pylori* infection[12]. Chronic inflammation causes proliferation of T-cells and B-cells due to antigen presentation. Malignant transformation occurs in a small percentage of B-cells and results in lymphoma, and the malignant process appears to be driven to a large degree by chronic *H. pylori* infection, because *H. pylori* eradication causes lymphoma regression in most cases[5]. However, four main chromosomal translocations, that is t (11; 18) (q21; q21), t (14; 18) (q32; q21), t (1; 14) (p22; q32), and t (3; 14) (p14.1; q32), reduce response to *H. pylori* eradication[13-14] and are found in 30% of cases. The most common translocation type is t (11; 18) (q21; q21). This type is more common in cases involving the lung or stomach, and is significantly associated with infections by CagA-positive strains[14].

**DIAGNOSIS OF GASTRIC MALT LYMPHOMA**

Median age at diagnosis is approximately 60 years and no gender predominance is shown. The most common presenting symptoms of MALT lymphoma are nonspecific dyspepsia and epigastric pain, whereas constitutional B symptoms and gastric bleeding are rare[15]. Other less common symptoms include nausea, vomiting, anorexia, weight loss, and early satiety[16]. Because these symptoms are nonspecific and are observed in other gastrointestinal disease, final diagnosis is made by endoscopic biopsy.

***Endoscopic evaluation***

Gastric MALT lymphomas are evaluated by esophagogastroduodenoscopy. The most common sites of involvement in the stomach are the pyloric antrum, corpus, and cardia, however, due to the possibility of multifocal involvement, biopsies should be taken from all abnormal and random sites, including the stomach, gastroesophageal junction, and duodenum[17,18]. Endoscopic appearances of MALT lymphoma varies, including erythema, erosions, and ulcers (Figure 1). Diffuse superficial infiltration is common, whereas masses are more common in diffuse large B-cell lymphoma[19]. Unlike benign ulcers and early gastric cancer, the erosions and ulcers of MALT lymphoma have an irregular or geographic appearance and multifocal characteristics. They may also exhibit irregular mucosal nodularities or only color changes. Thus, if lymphoma is doubted, biopsy is needed. Because some lymphomas infiltrate the submucosal layer without mucosal layer involvement, biopsies should be sufficiently deep and large enough for histopathologic and immunohistochemical analysis. Evaluations of *H. pylori* infection should include histology, rapid urease testing, urea breath testing, monoclonal stool antigen testing, or serologic studies.

***Pathologic evaluation***

Histologic diagnosis of primary gastric lymphoma is somewhat difficult because the endoscopic findings of lymphomas are indistinguishable from those of benign gastritis, and because they can involve the submucosal layer without mucosal involvement[20,21]. A correct histologic diagnosis after first endoscopy is made in 75% of low-grade and 79% of high-grade cases[19]; thus, suspicion is most important during endoscopic examinations, and multiple biopsies, including normal mucosa, are needed due to the possibility of multifocal lesions or combined cases of low and high-grade lymphoma.

The histologic characteristics of the low-grade MALT lymphoma are; centrocyte-like cell proliferation, plasma cell infiltration, and lymphoepithelial lesions defined as the unequivocal invasion and partial destruction of gastric glands or crypts. The key histologic feature of low-grade MALT lymphoma is the presence of a lymphoepithelial lesion[22,23] (Figure 2). However, lymphoepithelial lesions can sometimes be seen in the context of florid chronic gastritis, and can be present in other sites of both native and acquired MALT[24]. The tumor cells of low-grade MALT lymphoma are usually small- to medium-sized lymphocytes with moderately abundant cytoplasm and irregularly shaped nuclei resembling those of follicular center cells (centrocytes) and have been designated centrocyte-like (CCL) cells[23]. There is a continuous spectrum of lesions during the transition from *H. pylori*-associated gastritis to low-grade MALT lymphoma. The histologic scoring system of the Wotherspoon criteria is widely used in diagnosis of MALT lymphoma[5] and immunoglobulin heavy chain gene rearrangement analyses by PCR (polymerase chain reaction) are also used[25]. Southern blot or PCR for immunoglobulin heavy chain rearrangement can assist in revealing monoclonality and in prediction of later lymphoma development, however the presence of monoclonality alone does not allow for a diagnosis of lymphoma. Accordingly, molecular tests should always be considered in the context of histologic findings[26-31].

CCL cells of Gastric MALT lymphoma and marginal zone B cells in spleen, Peyer’s patches and lymph nodes have almost the same immunophenotype. Both types of cells are positive for surface immunoglobulins and pan-B antigens (CD19, CD20, and CD79a) and lack CD5, CD10, CD23, and cyclin D1 expression[24,32].

***Other evaluation***

If gastric MALT lymphoma is verified, other examinations, such as endoscopic ultrasound (EUS), bone marrow biopsy, standard posteroanterior and lateral chest radiographs, upper airway examination, and CT scans of chest, abdomen and pelvis, should be performed for staging. Of these, EUS is recognized as valuable for diagnosis and treatment of gastric MALT lymphoma. The EUS findings of MALT lymphoma are superficially spreading, diffusely infiltrating, mass forming, and mixed types. Superficially spreading and diffusely infiltrative types are unique forms of low-grade MALT lymphoma[33]. In addition, EUS-guided biopsies are helpful for histologic evaluations when endoscopic biopsies are insufficient[34,35] and for supplementation of false negative endoscopic biopsies[36,37]. EUS can determine depth of infiltration and detect the presence of enlarged perigastric lymph nodes[38-42]. In one study, EUS made a correct diagnosis of lymphoma with a sensitivity of 89%, specificity of 97%, and diagnostic accuracy of 95% and evaluation of lymphoma depth invasion with a sensitivity of 44%, specificity of 100%, and diagnostic accuracy of 77%[43,44]. In addition, EUS can be used for assessment of complete regression of MALT lymphoma after eradication of *Helicobacter pylori*. However, in this context, the effectiveness of EUS is controversial when verification of the presence or absence of a lesion is difficult due to atrophic changes caused by MALT lymphoma after *H. pylori* eradication[40]. Computed tomography is helpful for evaluation of lymph nodes on both sides of the diaphragm, but shows low sensitivity for detection of perigastric lymph node invasion[45]. Due to low fluorodexoyglucose (FDG) uptake, small lesion sizes, and slow progression, PET is not usually helpful[46-48].

**TREATMENT OF GASTRIC MALT LYMPHOMA**

Low-grade MALT lymphoma (stage IE1 by Musshoff’s modification of the Ann Arbor classification[49,50], that is, infiltration limited to mucosa and submucosa) can show complete regression after *H. pylori* eradication, and thus, surgery and chemotherapy options are held in abeyance until the effects of *H. pylori* eradication are known (Figure 3)[42,51]. Therefore, accurate diagnosis and staging are essential before initiation of treatment (Table 1). Most low-grade MALT lymphomas are limited to the mucosal or submucosal layers, and response to *H. pylori* eradication is decreased in cases of deeper involvement. Accordingly, evaluations of gastric wall involvement by EUS are important[42,52-53]. In general, MALT lymphoma shows slow progression and its prognosis is good when the disease is localized, before the terminal stage[54]. However, rate of progress to high-grade lymphoma accelerates with time, thus, early diagnosis and treatment is important.

***H. pylori* eradication**

Numerous studies have confirmed that gastric MALT lymphoma can show complete regression according to endoscopic, histologic, and molecular criteria after *H. pylori* eradication[52,55-58]; since the first such report was issued[5], other studies evaluating the effectiveness of *H. pylori* eradication in stage IE1 have reported complete remission rates of 60%-92%[5-7,59-64]. In general, patients who are positive for *H. pylori* are administered triple or quadruple *H. pylori* therapy for 1-2 wk[52,59-60], and then retested 4-8 weeks later. If this first-line therapy fails, bismuth-based quadruple therapy (excluding antibiotics previously taken) is recommended[1,2,65]. Reported prevalence rates of *H. pylori* negativity in gastric MALT lymphoma range from 0 to 38%[66,67]. However, several factors should be kept in mid, such as, after *H. pylori* eradication, recovery after *H. pylori* infection, non-*H. pylori* infection such as, *Helicobacter heilmannii* or *Helicobacter felis*, or autoimmune effects can cause false negative results for *H. pylori* in early gastric MALT lymphoma. Thus, overlapping tests for *H. pylori* infection and detailed history taking are needed. Although five patients showing negative test results for *H. pylori* who were cured after *H. pylori* eradication have been reported[68-70], it is controversial. Successfully treated cases after radiotherapy only have been reported[71], however further studies are needed.

***Treatment of high-grade MALT lymphoma***

Changes to high-grade MALT lymphoma result in proliferation regardless of *H. pylori* antigen, and correlation between increase of stage or histologic grade and decrease of *H. pylori* infection rates has been reported[11]. More than 80% of patients with stage IIE disease (lymphoma additionally infiltrating lymph nodes on the same side of the diaphragm) were reported to be cured after total gastrectomy[72], however, this technique has a marked effect on quality of life[73]. On the other hand, involved field radiotherapy at 30-40 Gy delivered in four weeks to the stomach and perigastric nodes was found to result in a complete remission rate of 90%-100% and a five-year disease-free survival rate of approximately 80%[74-76]. Radiotherapy is preferred in patients with advanced disease negative for *H. pylori* and in those with persistent disease after *H. pylori* eradication[77]. Other treatments include chemotherapy, immunotherapy, or combined chemoimmunotherapy. Immunotherapy with rituximab, a chimeric monoclonal antibody directed against B-cell-specific antigen CD20, was first demonstrated in patients with follicular lymphomas[78]. In addition, the therapeutic use of this antibody has been extended over recent years to other types of non-Hodgkin lymphomas, and it has shown good results as a single agent[78-80] or in combination with chemotherapy[81-84]. Rituximab is also effective in gastric MALT lymphoma resistant or refractory to antibiotics and negative for *H. pylori* infection[85,86]. If high-grade MALT lymphoma is positive for *H. pylori* infection, *H. pylori* eradication treatment should be administered, because the presence of *H. pylori* could aid recurrence, although the usefulness of eradication in such cases has been questioned.

***Follow-up***

Complete remission of low-grade MALT lymphoma after *H. pylori* eradication takes considerable time; thus, regular endoscopic follow-up is needed. Regression may be indicated by an area of whitish or discolored mucosa with a granular pattern[87,88]. Nevertheless, endoscopic findings can be nonspecific in recurrent cases; thus, endoscopic biopsies of normal and abnormal-looking gastric areas are needed. Median time to remission is five months, and is usually achieved within 12 mo, however, in some cases, time to remission has been reported to be as long as 45 months[55,.61,77]. Endoscopic examination with biopsies, tests for *H. pylori* infection, and EUS are recommended every three months until remission, and then every six months or annually for two years, however, the length of follow-up needed has not been determined[57,89]. Histologic remission of MALT lymphoma does not mean cure due to the possibility of false-negative result and of the survival of some malignant cells. Unfortunately, there is no unequivocal indicator of cure. A PCR test was recently devised for detection of tumor clones, and 50% of patients in clinical remission were found to have tumor clones by PCR. Furthermore, a decrease in clone counts was observed during continued follow-up[90]. In another study, these remnant malignant clones detected by PCR had disappeared at 12 mo[91]. Accordingly, a positive PCR result after achievement of histologic remission does not predict for subsequent relapse; thus, a long follow-up period is needed[58].

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**P-Reviewers:** Peter B, Sakata N **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**Figure 1 Variable endoscopic findings of gastric mucosa-associated lymphoid tissue lymphoma.** A: Single erosive type; B: Ulcerative type; C: Atrophic type; D: Cobblestone-mucosa type; E: Nodular type; F: IIc-like type.

**Figure 2 Histpathological and immunohistochemical features of gastric** **mucosa-associated lymphoid tissue lymphoma.** A: Histopathological finding; Gastric MALT lymphoma shows many lymphoepithelial lesions formed by the invasion of glands by centrocyte-like cells [hematoxylin and eosin (HE) stain, × 400]; B: Immunohistochemical finding. Centrocyte-like cells shows strong positive signals for CD20 (× 400).

**Figure 3 Ann Arbor staging system modified by musshoff and suggested therapeutic algorithm for gastric mucosa-associated lymphoid tissue lymphoma.**

**Table 1 Staging systems of gastric mucosa-associated lymphoid tissue lymphoma**

|  |  |  |  |
| --- | --- | --- | --- |
| **Lugano staging system for gastrointestinal lymphoma** | **TNM staging system modified for gastric lymphoma** | **Ann Arbor staging system modified by Musshoff** | **Tumor involvement** |
| I = Confined to GI tract (single primary or multiple, noncontiguous) | T1 N0 M0 | IE1 | Mucosa, submucosa |
|
| T2 N0 M0 | IE2 | Muscularis propria |
| T3 N0 M0 | Serosa |
| II = Extending into abdomen |  | | |
| II1 = local nodal involvement | T1-3 N1 M0 | IIE1 | Perigastric lymph nodes |
| II2 = distant nodal involvement | T1-3 N2 M0 | IIE2 | More distant regional lymph nodes |
| IIE = penetration of serosa to involve adjacent organs or tissues | T4 N0 M0 | IE | Invasion of adjacent structures |
|
| IV = disseminated extra-nodal involvement or concomitant supradiaphragmatic nodal involvement | T1-4 N3 M0 | IIIE | Lymph nodes on both sides of the diaphragm |
| T1-4 N0-3 M1 | IVE | Distant metastases (e.g., bone marrow or additional extranodal sites) |

GI: Gastrointestinal; TNM: Tumor node metastasis.