

Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

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ABSTRACT

The connection between *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue (MALT) lymphoma is well established. *H. pylori* infection causes an immunological response, leading to chronic gastritis with formation of lymphoid follicles within the stomach. These lymphoid follicles resemble nodal tissues found throughout the body and are composed of reactive T cells and activated plasmal cells and B cells. The B cells are responsible for initiating a clonal expansion of centrocyte-like cells that form the basic histology of MALT lymphoma. Early diagnosis of MALT lymphoma is difficult but essential for adequate treatment. Clinical symptoms are vague and varied, with abdominal pain being a common presenting complaint. The endoscopic appearance of this tumor is varied and can be infiltrative, exophytic, or ulcerative. In addition, the tumor can have a multifocal distribution, and therefore aggressive tissue sampling is crucial for diagnosis. Endoscopic ultrasound is essential to document the extent of disease and is more accurate than CT scan in detection of spread to perigastric lymph nodes. Lesions that are confined to the mucosa or submucosa of the gastric wall are believed to be dependent on *H. pylori* stimulation and therefore can be successfully treated with *H. pylori* eradication. Those MALT lymphomas that present at more advanced stages require more aggressive management and can be treated with surgical resection, radiation, or chemotherapy. Follow-up is critical in all patients who have been treated with *H. pylori* eradication and consists of multiple endoscopic biopsies for histological and molecular studies as well as endoscopic ultrasound at 3, 6, and 12 months after treatment. The reappearance of MALT lymphomas has been seen years after treatment, and therefore follow-up of these patients should be indefinite. (Am J Gastroenterol 2003;98:975–986. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Primary gastric lymphoma (PGL) is an uncommon entity, accounting for 1–5% of all malignant disorders of the stomach (1). The majority of PGLs are B cell non-Hodgkin's lymphomas, either low grade mucosa-associated lymphoid tissue (MALT) lymphoma or a high grade, diffuse, large cell

lymphoma. Although rare, non-Hodgkin's lymphomas of the GI tract, particularly the stomach, represent 52% of all extranodal lymphomas (2, 3).

In 1983, Isaacson and Wright classified PGLs as a distinct entity from previously classified nodal lymphomas (4). PGLs are believed to arise from MALT that is found in Peyer's patches. A benign reactive process in response to an inciting antigen leads to the formation of lymphoid follicles that are populated by B cells at various stages of development. At this stage, the tissue may be referred to as *reactive lymphoid hyperplasia* or *pseudolymphoma*. As progression continues, there is formation of a diffuse cellular infiltrate of small centrocyte-like cells that arise from the marginal zone of the lymphoid follicle and invade the epithelial lining, forming classic lymphoepithelial lesions (5). These cells stimulate a monoclonal population of B cells that is still dependent on the inciting antigen, a characteristic shared by low grade lymphomas at a wide variety of extranodal sites, including salivary glands, thyroid, and lung, and is collectively referred to as *MALT lymphoma* or *low grade MALToma* (6). In PGL, the inciting antigen is largely thought to be *Helicobacter pylori*, which initially provokes the host's immune system. Treatment with an anti-*H. pylori* regimen at this point is postulated to aid in the regression of this tumor. On the other hand, some patients present with high grade PGLs, in which the infiltrate consists of large centroblast-like cells that do not necessarily form the classic lymphoepithelial lesions seen in low grade PGL. This tumor produces a monoclonal B cell clone that may not be dependent on the antigenic stimuli that triggered the initial chain of events (5). Although *H. pylori* may have initiated the formation of this tumor, the autonomous nature of high grade PGL makes it largely unresponsive to *H. pylori* therapy.

The relationship between low grade MALT lymphoma and high grade B cell lymphoma of the stomach is still controversial. However, high grade gastric lymphomas probably represent a progression from low to high grade PGL. A close relationship between the two entities is suggested by the frequent presence of foci of both grades of lymphoma in the same lesion (7) and the high frequency of the same cryptogenic abnormality (8), suggesting this transformation from low to high grade. Clinically, however, they

behave very differently. Low grade MALToma presents at an early stage, grows slowly, and can remain localized for years. It has an excellent prognosis, with long term survival the rule (9). In contrast, high grade PGLs, as well as secondary gastric lymphomas, demonstrate less favorable behavior and are more difficult to cure (10).

GASTRIC MALT LYMPHOMA AND *H. PYLORI*

Lymphoid tissue is absent from the normal stomach. Lymphoid follicles appear in the stomach after *H. pylori* infection, with resultant chronic gastritis (11). This accumulation of lymphoid tissue in the stomach as a result of chronic *H. pylori* gastritis forms the soil from which low grade gastric MALToma emerges, accounting for the paradoxically frequent occurrence of lymphoma in the stomach despite the lack of native MALT in this organ (12, 13).

Several lines of evidence suggest that gastric lymphoma arises from *H. pylori*-associated MALT. First, *H. pylori* can be demonstrated in the gastric mucosa of more than 90% of patients with gastric MALT lymphoma (10, 12). Wotherspoon *et al.* showed that *H. pylori* was present in 101 of 110 patients (92%) with gastric MALT lymphoma (12). Second, Doglioni *et al.* showed an epidemiological association between the incidence of *H. pylori* infection and the incidence of PGL (14). In Feltre, Italy, a geographic region with a high incidence of gastric lymphoma, there was a high prevalence of gastritis associated with *H. pylori* infection (87%). In contrast, in three areas of the United Kingdom where gastric lymphoma was uncommon, the rate of *H. pylori* infection was significantly lower (50–60%). The incidence of gastric adenocarcinoma, which has also been associated with chronic *H. pylori* infection, was also substantially higher in Feltre than in the UK (270/100,000 vs an average of 82/100,000 population/5 yr), further implicating *H. pylori* as a carcinogen. Parsonnet *et al.* demonstrated the association between *H. pylori* and PGL in a case-control study involving two large cohorts (15). They found that patients with gastric lymphoma were more likely to have evidence of infection with *H. pylori* than were matched controls (relative risk 6.3). Infection with *H. pylori* also preceded the onset of gastric lymphoma. Eighty-five percent of cases harbored *H. pylori* antibodies in sera collected 15 yr earlier, compared with 55% of controls and 65% of those with nongastric lymphomas (15).

More direct evidence confirming the importance of *H. pylori* infection in the pathogenesis of gastric lymphoma has been obtained from a series of *in vitro* studies. In 1993, Hussel *et al.* studied the immunological response of low grade MALT lymphoma after exposure to specific *H. pylori* strains. They found a proliferation of *H. pylori*-specific T cells that subsequently led to an increase in tumor immunoglobulin and interleukin (IL)-2 release. Likewise, *H. pylori* removal caused a decrease in IL-2 expression (16). This study directly implicated *H. pylori* as an important force in the pathogenesis of primary gastric MALT lymphoma.

Regression of MALT lymphoma in response to *H. pylori* eradication strengthens the theory of a cause and effect relationship. A pilot study by Wotherspoon *et al.* first documented tumor regression lasting up to 22 months after the cure of *H. pylori* infection in five of six patients with early stage, low grade gastric MALT lymphoma (17). This observation was confirmed by Roggero *et al.* in a study of 26 patients with low grade MALT lymphoma. After complete eradication of *H. pylori*, total regression of lymphomatous tissue was documented in 15 of 25 patients with a 12-month follow-up (18). Although rare, there have also been reports of high grade diffuse B cell lymphoma of the stomach and duodenal MALT lymphoma regressing after *H. pylori* treatment (19).

H. pylori infection may also be responsible for concurrent gastric and intestinal MALT lymphomas that have increasingly been identified (20). In one study, rearranged Ig genes from six cases with concurrent gastric and intestinal MALT lymphomas were cloned and sequenced, and it was shown that concurrent gastric and intestinal MALT lymphomas are derived from the same clone (21). The intestinal lesions may have resulted from the dissemination of gastric tumors, and antigenic stimulation may have played a role in their development. It is postulated that *H. pylori* treatment may be beneficial in these tumors. In addition, MALT lymphomas have been shown to disseminate preferentially to other mucosal sites without systemic spread (22, 23). Further studies will need to investigate *H. pylori* treatment in these rare cases.

The great majority of individuals infected with *H. pylori* remain asymptomatic. The differences in clinical outcomes have been attributed to multiple factors, including the genetic background of the host, environmental factors, and virulence factors of different bacterial strains (16). Numerous studies have focused on examining different antigens and proteins related to *H. pylori* to discover strains responsible for progression to malignancy.

H. pylori strains are subdivided into two different major types according to the expression of cytotoxin-associated antigen (CagA) (24). Strains expressing the CagA protein (CagA+ strains) have been strongly associated with severe gastritis, duodenal ulcers (25–30), and gastric adenocarcinoma (31, 32). Strains expressing the CagA protein also seem to play a crucial role in the pathogenesis of gastric MALT lymphoma. Eck *et al.* reported a very high correlation of CagA+ *H. pylori* with gastric MALT lymphoma (33). Comparing CagA status in 68 patients with MALT of all grades and 49 patients with *H. pylori* gastritis by immunoblotting techniques, they found that 95% of lymphoma patients, compared with 68% of *H. pylori* gastritis patients, were positive for CagA, supporting the role of CagA+ strains of *H. pylori* in the development of MALT lymphomas.

Other studies, however, using similar serological methods do not support this correlation. Crabtree *et al.* showed an equal frequency of CagA+ and CagA- serology in patients

with gastric MALT lymphoma, healthy volunteers, and patients with dyspeptic disease (34). Similar results were obtained independently by Forester *et al.* (35) and Witherell and Parsonnet (36).

There is growing evidence of genetic diversity among *H. pylori* strains that could account for differences in clinical outcomes. In an effort to identify a marker of *H. pylori* strains associated with severe clinical sequelae, Chang *et al.* attempted to identify an antigen specific to *H. pylori* strains associated with gastric MALToma using immunoscreening techniques (37). Membranous and secreted proteins of *H. pylori* strains from 17 patients with MALT lymphomas were compared with the proteins of *H. pylori* strains from 42 control patients. A 19-kD secreted protein was identified in all *H. pylori* strains from MALToma patients by Western blot, which was uncommon in strains from patients with other *H. pylori*-associated diseases. When the protein was purified and sequenced, it was found to be an FldA (flavodoxin A) homologue protein. Nucleotide sequencing of the FldA gene in the *H. pylori* strains from patients with MALToma and controls revealed that a nucleotide G insertion at position 481 of the FldA gene was conserved more frequently in *H. pylori* strains of MALToma patients than in the strains found in patients with other diseases (nine of nine vs six of 17; $p = 0.002$). Antibodies to recombinant FldA protein were tested in serum samples from patients and controls, and 12 of the 17 sera from MALToma patients were positive for antibody to the recombinant protein, whereas only seven of the 42 control sera were positive ($p < 0.0001$). These results suggest that truncated FldA could be specifically associated with gastric MALToma, and antibody to this antigen could be used as a serological marker of the disease.

In another study, Kawahara *et al.* examined antibodies to HGC-27 human gastric epithelial cells and human recombinant heat shock protein (Hsp) 60 using ELISA and immunoblotting in sera obtained from *H. pylori*-positive patients with MALToma ($n = 11$) or other GI diseases (peptic ulcer, $n = 40$; nonulcer dyspepsia, $n = 20$) and *H. pylori*-negative healthy control subjects ($n = 10$) (38). They demonstrated that anti-HGC-27 antibodies are often increased in MALToma patients, and host Hsp60 is a major target antigen. Moreover, the antibodies also detected a band found in *H. pylori* extracts called HspB. They concluded that antibodies against *H. pylori* HspB cross-react with Hsp60, leading to the elevated antibody levels seen in MALT lymphoma patients (38). A few *H. pylori*-infected patients with gastric diseases other than MALToma also had elevated IgG titers to HspB and Hsp60. The authors are carefully following these patients to see whether they will develop gastric MALToma.

It is theorized that, although *H. pylori* appears integral for initial MALT development, eventually its antigenic stimulation is no longer necessary for MALT progression. Genetic changes may be involved in the final abnormal proliferation of monoclonal B cells seen in high grade

lymphomas. Wotherspoon *et al.* suggest that after the accumulation of lymphoid cells in the stomach in response to *H. pylori* infection, genetic abnormalities in host B cells, possibly trisomy 3, lead to the development of monoclonal proliferation and low grade lymphoma (8). This proliferation of monoclonal B cells is thought to remain dependent on the antigenic stimulation by *H. pylori* and the production of IL-2 by non-neoplastic cells. Further genetic rearrangements lead to the development of B cell proliferation that is independent of *H. pylori* antigen. In addition, Neumister *et al.* attempted to detect p16 deletions in MALT lymphomas by polymerase chain reaction (PCR) assay (39). They showed that homozygous deletions were found in 2/14 (14%) of high grade gastric MALT lymphomas, compared with none in *H. pylori*-related gastritis and low grade MALT lymphomas. Last, Horsman *et al.* describe an increased frequency of translocation t(11,18) in patients with lymphoma, again implicating genetic abnormalities in the progression of MALT lymphomas (40).

CLINICAL FEATURES

Clinically, the challenge with gastric MALT lymphoma is to make the diagnosis early enough to prevent tumor progression from low to high grade with a simple course of antibiotic therapy. However, this may not be so easy. Patients may be asymptomatic, or signs and symptoms may be nonspecific and overlap with those of peptic ulcer disease. Epigastric pain develops insidiously and may be present for months to years before a diagnosis is made. Abdominal pain was the presenting complaint in large series from both Saudi Arabia (41) and France (42). In the French study, Ruskone-Fourmestreaux *et al.* found that the onset of pain preceded the diagnosis by 3 yr (42). Symptoms such as abdominal pain and vomiting are more likely to be associated with MALT lymphomas than with secondary nodal lymphoma. Other symptoms indicating more advanced disease overlap with those of gastric carcinoma, including anemia, weight loss, and GI bleeding (42). In patients with these symptoms, there should be a high index of suspicion for MALT lymphoma, and early endoscopy with biopsy is indicated for diagnosis.

ENDOSCOPIC APPEARANCE

Several authors have described the endoscopic appearance of PGL (43, 44). Three main endoscopic patterns can be recognized: a tumor-like appearance with a polypoid mass (exophytic type) (Fig. 1A, 1B); ulceration or multiple small erosions (ulcerative type) (Fig. 1C); and hypertrophic type with large, nodular, sometimes giant folds (Fig. 1D). However, these descriptions are not specific for PGL, and the endoscopic diagnosis may range from gastritis to carcinoma. Taal *et al.* evaluated endoscopic characteristics in a series of 114 patients with PGL (43). In low grade lymphoma, endoscopic findings were often interpreted as a benign condition (25 of 51), in contrast to high grade lymphoma, for

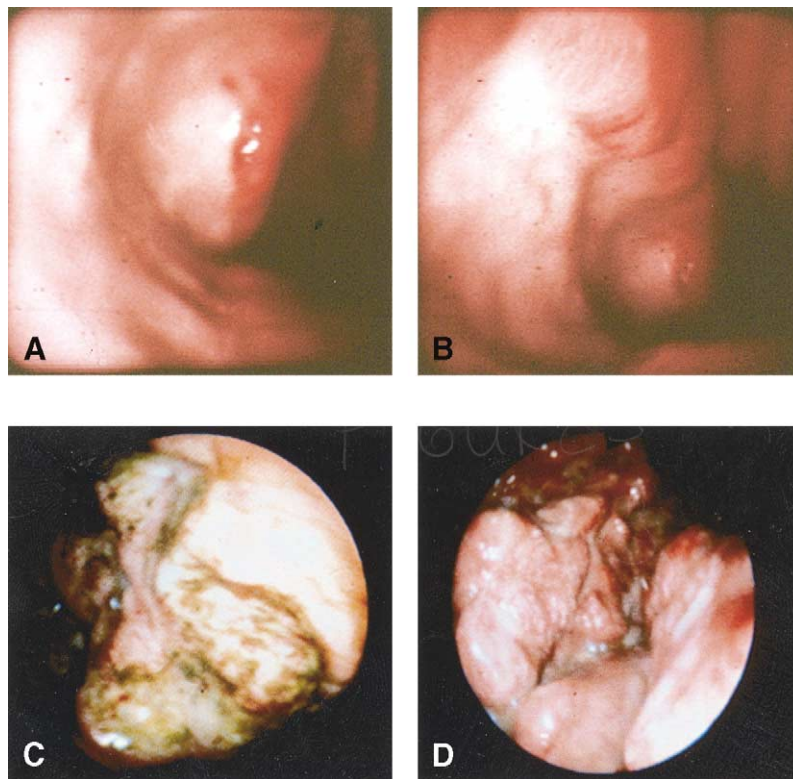


Figure 1. Endoscopic appearances of MALT lymphoma. (A, B) Exophytic type. Large, friable, nodular mass with evidence of bleeding that is located in the antrum of the stomach. This lesion proved to be a MALT lymphoma. (C) Ulcerated type. An ulcerated MALT lymphoma with large confluent ulcers covered with exudate. (D) Hypertrophic type. Hypertrophic, edematous, irregular folds are present in the proximal stomach and persist despite maximal insufflation.

which carcinoma was the most frequently (37 of 63) suspected diagnosis.

PGL and secondary gastric lymphoma can also be differentiated by endoscopic growth pattern. This distinction is important because these tumors differ in pathogenesis, treatment, and prognosis. Secondary gastric lymphoma generally presents as advanced, disseminated, non-Hodgkin's lymphoma requiring chemotherapy for treatment. On the other hand, PGL manifests as early, localized disease with a high potential for cure. Kolve *et al.* studied 176 patients with PGL and 29 patients with secondary gastric lymphoma in an attempt to evaluate differences in their endoscopic features. They found that in both groups the predominant site of tumor invasion occurred in the antrum and body of the stomach. However, in secondary gastric lymphoma multifocal tumor involvement, which also included the fundus or duodenum, was common and occurred in 52% and 33%, respectively. Conversely, in PGL unifocal tumor growth predominated, with additional involvement of the fundus and duodenum occurring only 19% and 11% of the time, respectively. The macroscopic appearance of the tumor may also aid in distinguishing between PGL and secondary gastric lymphoma. Tumors with bulky disease greater than 5 cm are more likely to represent high grade PGL than either low or high grade secondary gastric lymphomas. Interestingly, the majority of low grade PGLs behave similarly to

secondary gastric lymphomas, with diffuse submucosal tumor infiltration rather than bulky disease (45).

DIAGNOSIS

Routine biopsies may miss the diagnosis in a significant number of patients. In a study by Taal *et al.*, a correct histological diagnosis after the first endoscopy was made in 75% of the low grade and 79% of the high grade cases (5). In low grade lymphoma, repeat endoscopy with biopsies was more frequently needed for correct diagnosis. Clearly, more aggressive tissue sampling, with multiple biopsy specimens of endoscopically abnormal and normal mucosa, should be taken from different gastric sites. This is particularly important in view of the possible multifocal distribution of the tumor and potential foci of high grade lymphoma. Special endoscopic biopsy techniques have been recommended for enhanced tissue diagnosis, including the following:

1. Snare biopsy if there are thickened or giant folds or a polypoid mass;
2. Saline-assisted mucosal resection (strip biopsy) if the lesion is flat or too firm to remove safely by snare (46);
3. Jumbo biopsy forceps to reach the deeper mucosal layers.

Table 1. Endoscopic Ultrasound Staging of Gastric MALT Lymphoma

T1a: Superficial mucosa: includes the first (hyperechoic) layer
T1b: Deeper mucosa to muscularis mucosa: includes up to the second (hypoechoic) layer
T2: To submucosa: includes the third (hyperechoic) layer
T3: Beyond submucosa: includes the fourth layer corresponding to the muscularis propria and the fifth layer corresponding to the serosa

In a Japanese series of eight patients, strip biopsy provided larger tissue biopsy specimens of 1.0–2.5 cm (47).

Brush cytology may provide some additional benefit (47). Other methods to improve the diagnostic yield of endoscopic biopsy specimens include the use of immunohistochemical techniques (48), as well as PCR assays to detect monoclonal B cell populations (49). Since the introduction of these techniques, problems in differentiating high grade lymphoma from adenocarcinoma have largely been solved.

Endoscopic Ultrasound Diagnosis

Endoscopic ultrasonography (EUS) has proven to be a beneficial procedure in the staging of PGL (Table 1). EUS has been able to predict histological features of the tumor, distinguish the depth of intramural tumor infiltration, detect metastasis to perigastric lymph nodes, and evaluate tumor regression after treatment (50–54).

Suekane *et al.* compared EUS appearance in PGL with histological features (53). Fifteen patients were divided by EUS patterns into superficial spreading, diffuse infiltrating, mass-forming, and mixed types. The nine patients that were characterized as superficial spreading or diffuse infiltrating had a low grade histology. The six patients with mass-forming or mixed type lesions had either a diffuse large cell or mixed histology (53). This study established a correlation between EUS findings and the histology of low and high grade gastric lymphomas.

Levy *et al.* used EUS to differentiate lesions based on thickness of the gastric wall (54). They characterized the gastric wall as normal, having mild intramural thickening (5 mm), or having severe thickening (6–12 mm). They were able to confirm the presence of a superficial early stage MALT lymphoma without tumor infiltration of the gastric wall. This pattern was present in all 15 patients, with no lesions extending beyond the muscularis propria or into adjacent lymph nodes. Although only a small number of patients were studied, these observations confirm similar results from previously published studies (53, 55). Levy *et al.* suggest that a histological diagnosis of low grade MALT

lymphoma should be questioned if there is massive infiltration and/or suspected metastatic lymph nodes at EUS (54).

EUS can also accurately predict how the tumor will respond to *H. pylori* eradication. In one prospective study, 12 of 14 patients in whom the MALToma was restricted to the gastric mucosa or submucosa, T1+T2 or EI1 according to the Ann Arbor classification (Table 2), had complete regression of the tumor within 14 months of *H. pylori* eradication. In contrast, zero of eight patients with lymphoma infiltrating muscularis or serosa (T3 or EI2) showed regression after cure of infection, confirming the lack of efficacy of *H. pylori* eradication except in early stage, low grade tumor (T1, T2 or EI1) (56). Therefore, EUS has proven beneficial in diagnosing, staging, and predicting the outcome in patients with MALT lymphoma.

Histological Diagnosis

In biopsy specimens, the hallmark of MALT lymphoma is the lymphoepithelial lesion that results from tissue invasion by atypical lymphocytes as well as reactive lymphoid follicles. Approximately one third of cases show plasma cell differentiation that is typically segregated beneath the surface epithelium. Tumor cells diffusely expand the lamina propria and grow around reactive follicles, which are most commonly located immediately above and beneath the muscularis mucosa. In addition to invading and destroying epithelial structures to produce characteristic lymphoepithelial lesions, tumor cells can colonize reactive follicles. As a result, neoplastic small cells can replace germinal centers, or the invading neoplastic cells can either undergo prominent plasma cell differentiation or produce a marked increase in large cells. The centrocyte-like or monocytoid cells with cleaved or irregular nuclei are indicative of atypia (Fig. 2A). In advanced lesions, with high grade components, large centroblast-like cells are present, with the classic lymphoepithelial lesions only rarely being seen (Fig. 2B) (5).

Zuckerberg *et al.* quantitatively analyzed the frequency of histological features in low grade lymphomas to determine their discriminant power in distinguishing low grade lym-

Table 2. Ann Arbor Classification of Extranodal Lymphoma (Modified by Musshoff)

EI: Lymphoma restricted to GI tract on one side of diaphragm
EI1: Infiltration limited to mucosa and submucosa
EI2: Lymphoma extending beyond submucosa
EII: Lymphoma additionally infiltrating lymph nodes on same side of diaphragm
EII1: Infiltration of regional lymph nodes
EII2: Infiltration of lymph nodes beyond regional nodes
EIII: Lymphoma infiltrating GI tract and/or lymph nodes on both sides of diaphragm
EIV: Localized infiltration of associated lymph nodes together with diffuse or disseminated involvement of extra-GI organs

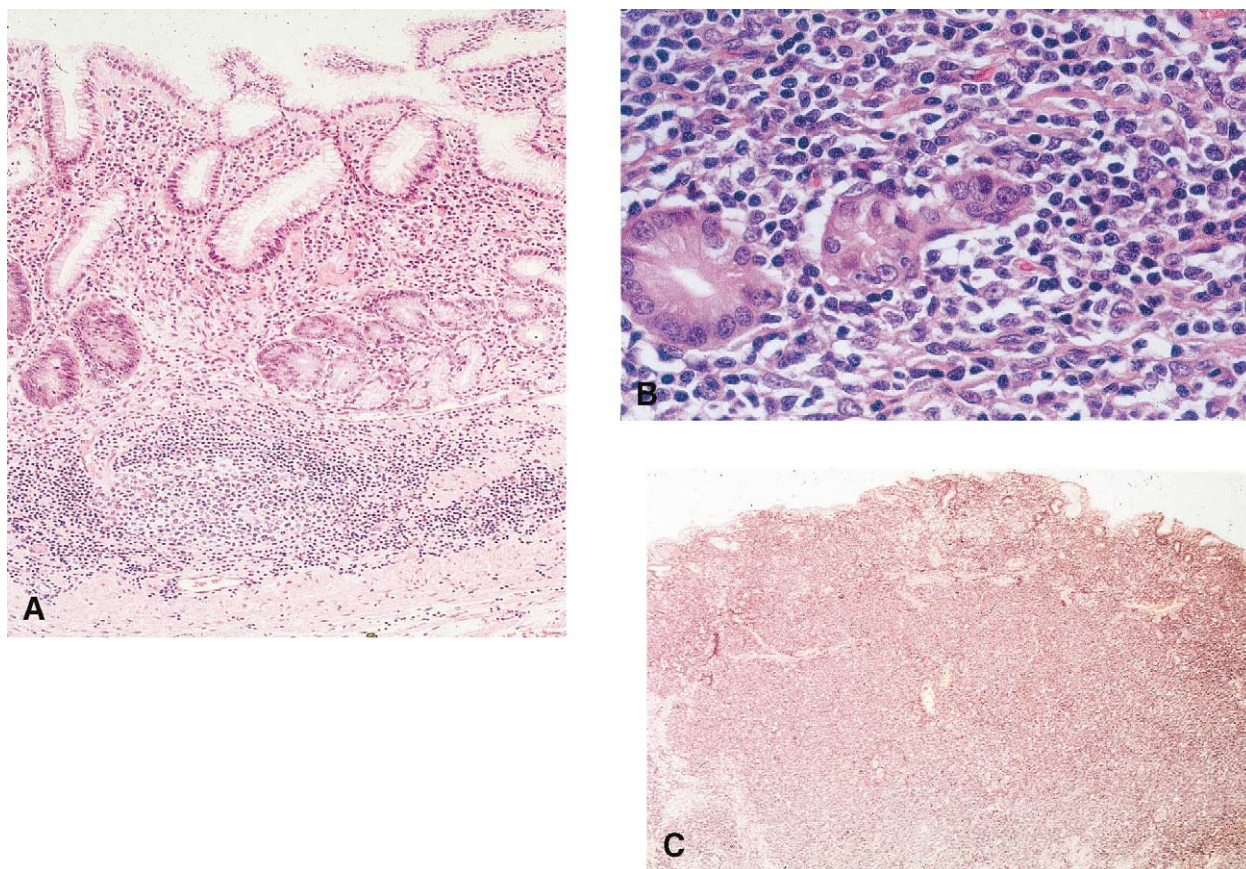


Figure 2. (A) Diffuse infiltrate of small centrocyte-like cells that form the classical lymphoepithelial lesions of low grade MALT lymphoma (5). (B) High grade lymphoma with lymphomatous infiltrate extending beyond the mucosa into the gastric wall. (C) Antral biopsy of chronic *H. pylori* gastritis. Note the abundant inflammatory reaction as well as the presence of lymphoid aggregates not normally present in the stomach.

phoma from gastritis (57). They found that a dense lymphoid infiltrate with prominent lymphoepithelial lesions, moderate cytological atypia, or Dutcher bodies (prominent intranuclear pseudoinclusions that were periodic acid-Schiff positive [Diastase-resistant] or immunoglobulin positive with immunostaining), seen in 72% of cases, is highly suggestive and may be diagnostic of lymphoma. Dense lymphoid infiltrates alone, however, were not a reliable marker of lymphoma, as 8.6% of benign lesions had lymphocytic infiltrate of similar density. Invasion of the muscularis mucosa was seen in all lymphomas but also in about 455 cases of benign infiltrates. The presence of germinal centers, crypt abscesses, and reactive epithelial atypia had no diagnostic utility.

In the past, most low grade MALT lymphomas of the stomach were known as *pseudolymphomas* or *lymphoreticular hyperplasia* because of the presence of reactive follicles and mixed inflammatory cell infiltration histologically and their slow growth and favorable prognosis clinically (58, 59). Lesions that were not low grade MALTomas were probably cases of *H. pylori* gastritis with exuberant reactive lymphoid hyperplasia, sometimes adjacent to a peptic ulcer (Fig. 2C). In a study of 97 cases formerly diagnosed as

pseudolymphoma, Abbondanzo *et al.* found that 77 (79%) were malignant lymphomas, including 51 MALTomas (60). The remainder included reactive lymphoid hyperplasia associated with chronic follicular gastritis (15 cases) and atypical lymphoid infiltrates (five cases). Differentiation between exuberant *H. pylori* gastritis and MALT lymphoma is not usually difficult. Problems arise, however, if the histology looks malignant but the infiltrate is polyclonal or the specimen looks benign histologically but the PCR pattern is monoclonal.

Genta and Graham recommend that you suspect the presence of a MALToma whenever the lymphoid infiltrate of *H. pylori* gastritis does not look typical (61). Rigorous histopathological criteria should be applied to the interpretation of gastric biopsies with atypical lymphoid aggregates and, if necessary, the diagnosis should be confirmed by an experienced histopathologist. Mucosa adjacent to MALT lymphoma also may show signs of chronic damage, and evidence of intestinal metaplasia, atrophy, and erosions has frequently been seen (62). Additionally, involvement may be multicentric, which may not be apparent on endoscopy, and large cell transformation can be focal and missed with resultant delay in appropriate treatment. Therefore, the

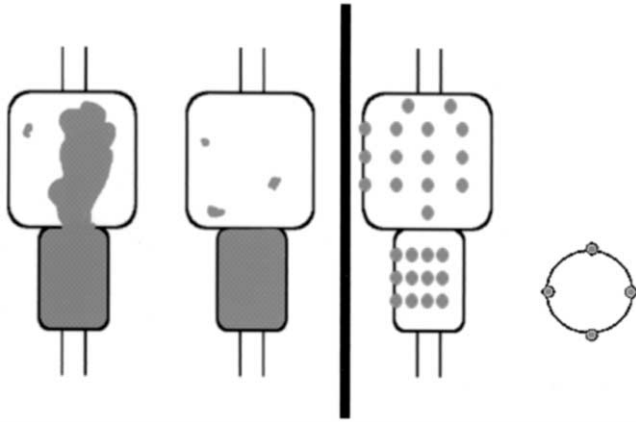


Figure 3. On the left, the multicentric origin of MALT lymphoma found in some patients. This patchy distribution may not be apparent on endoscopy and can be missed. On the right, a proposed endoscopic biopsy protocol that extensively maps the stomach. The numerous biopsy specimens can aid in determining the extent and nature of a lesion.

stomach should be mapped with multiple biopsies as recommended by Genta and Graham (Fig. 3) (61).

MOLECULAR BIOLOGY

The genetic features of these tumors are still being explored. The phenotype and molecular biology of MALTomas also, at times, distinguish these tumors from other lymphomas. MALTomas are B cell lymphomas with a monocytoid or centrocyte type morphology. They are derived from marginal zone parafollicular cells rather than follicular center cells. Phenotypically, MALTomas are CD5- and CD10-negative. BCL-2 genes, typically rearranged in follicular lymphoma, are germline in MALTomas. However, Villuendas *et al.* have shown increased expression of BCL-2 protein in low grade MALTomas and loss of its expression in high grade lymphomas (63). Alterations in p53 are also thought to be involved in neoplastic development and progression in MALTomas. Du *et al.* found p53 mutations in 6.8% of cases of low grade MALTomas and in 18.8% of high grade lymphomas (64). Loss of p53 heterozygosity was seen in only 9% of low grade lymphomas showing p53 abnormalities but was present in 67% of high grade lymphomas showing p53 mutations. Although changes in p53 are not specific for MALTomas, p53 mutations in MALT lymphomas follow a common theme in histological progression or transformation of lymphoma from low grade to intermediate to high grade disease. The most common detectable cytogenetic abnormality is trisomy 3, which is found in 60% of cases of MALToma (65).

Finally, replication error (RER+) phenotype (a manifestation of genetic instability) was detected in one half of both low grade MALTomas as well as in high grade tumors. The same cases were investigated for p53 mutation, which was found in 25% of the total cases. These mutations were

statistically related to RER+ phenotype ($p < 0.05$), suggesting that genetic instability occurs throughout the spectrum of lymphoma development and may be related to the accumulation of genetic aberrations, such as p53 mutations. Observation of identical microsatellite alterations between the adjacent lymphoid infiltrates and their corresponding lymphomas provides genetic evidence for evolutionary link of the two lesions. The homogenous microsatellite alterations observed between low and high grade components indicate their clonal lineage and genetic diversity (66).

RADIOLOGY

If an early stage, low grade MALT lymphoma is suspected, both CT scan and EUS should be performed before initiation of antibiotic therapy for *H. pylori* infection. Conventional radiography by single or double contrast upper GI series is not recommended because findings are often nonspecific. In a retrospective study of 25 patients with proven low grade gastric MALToma, Kim *et al.* found that disorganized, convergent rugae, vague ulcer margins, and multiplicity of lesions were helpful in differentiating MALTomas from gastric carcinomas or gastritis (67).

CT scan is recommended to evaluate lymph nodes above and below the diaphragm but has very low sensitivity for the detection of perigastric lymph nodes (68). As noted earlier, EUS is the procedure of choice to assess the size and depth of the lesion and the presence of perigastric nodes.

THERAPY

The connection between *H. pylori* and low grade gastric MALT lymphomas is strong, and therefore treatment strategies are aimed at *H. pylori* eradication in early tumor stages. Numerous studies have evaluated *H. pylori* eradication in stage EII and documented complete regression of low grade gastric MALT lymphomas in 50–100% of all patients, with a disease-free survival time of greater than 6 yr post-therapy (69). In large studies, patients with documented stage EII disease are tested for *H. pylori* by endoscopy with multiple gastric biopsies. Those patients that test positive are treated with a standard regimen of *H. pylori* therapy, and follow-up endoscopy is repeated 1–2 months later to document *H. pylori* eradication. Alternative therapy with three to four drugs is given for patients who remain *H. pylori* positive despite initial therapy, and follow-up endoscopy with biopsy is again done 1–2 months later. This strategy continues until *H. pylori* is fully eradicated (69, 70). In a study of 48 low grade MALT lymphoma patients who were *H. pylori* positive, eradication occurred in 38 patients after one course of *H. pylori* therapy, six patients after two courses of therapy, and three patients after three courses of therapy. In this study, complete eradication of *H. pylori* could not be obtained in one patient despite five different treatment regimens. On the other hand, other studies have documented 100% *H. pylori* eradication after only one reg-

imen (71). Patients who are *H. pylori* negative by biopsy should have *H. pylori* serology drawn because of the potential for false negative results in people recently treated with either proton pump inhibitors or antibiotics (72).

The time between *H. pylori* eradication and complete remission of gastric MALT lymphoma can vary and can take longer than 12 months (73). Therefore, patients are evaluated every 6 months for the first 2 yr, then yearly with endoscopy and biopsy to monitor histological regressions (70, 74). In the German MALT Lymphoma Study Group, the largest MALT treatment study to date, 120 patients with stage E11 low grade MALT lymphoma were treated with *H. pylori* eradication and followed. Treatment failure was considered if a partial regression of the tumor was present at 26 wk or no tumor regression was apparent at 12 months post-*H. pylori* eradication. After a mean follow-up period of 48 months, 81% of patients were in complete remission, 9% were in partial remission, and 10% were nonresponders (69). In a French study of 48 stage E11 low grade MALT lymphoma patients, 69% of patients were in complete remission at 6 months after *H. pylori* therapy (75). An American trial of 34 patients reported a 50% complete remission rate after a mean follow-up of 41 months (range, 19–70 months) in patients with disease confined to the mucosa or submucosa (76). An Italian study documented histological regression of tumor in 47 patients treated with *H. pylori* eradication alone (77). Overall, more than 20 studies have been reported with similar success rates (69).

The treatment of high grade gastric MALT lymphomas presenting at E11 are more controversial. Because high grade lymphomas are believed to progress from an initial low grade lesion that is dependent on *H. pylori* stimulation, treatment with *H. pylori* eradication may be beneficial in a subset of these patients. Regression of high grade lymphoma has been documented in scattered reports, with sustained response seen at 14 months (78). Follow-up is needed in these patients to document long term survival, and sole therapy with *H. pylori* eradication is not advocated. Surgery and radiation are still the main focus of treatment in this subset of patients.

Prognostic factors for predicting tumor regression with *H. pylori* eradication have been studied. Important positive prognostic indicators include tumor confined to the submucosa and negative involvement of perigastric lymph nodes as documented by EUS (71, 72). Interestingly, tumor width does not predict response rate, and in a study by Levy *et al.* the patient with the largest tumor, measuring 10 cm, experienced a complete remission with *H. pylori* eradication alone (70). In addition, *H. pylori* positivity and distal or diffuse location of the tumor in the stomach were positive characteristics, whereas *H. pylori* density by biopsy had no prognostic relevance (79). Molecular markers may be able to predict tumor response to *H. pylori* therapy. Tumors with a t(11,18) rearrangement may represent a more aggressive tumor with possible conversion to a high grade lymphoma (79). *H. pylori* eradication in these tumors is less likely to

result in a complete remission. The percentage of CD19- and CD20-positive B lymphocytes in the tumor is also a prognostic indicator. Tumors with less than 50% of CD19- and CD20-positive cells are more likely to undergo complete remission with *H. pylori* eradication alone. Tumors with greater than 50% CD19- and CD20-positive cells may be undergoing transformation to a more advanced, aggressive tumor, and *H. pylori* eradication alone is unlikely to result in complete remission (80).

MALT lymphomas, of either low or high grade, that are stage E11 and are not *H. pylori* positive or do not respond to antibiotic therapy can be treated with surgery, radiation, or chemotherapy. Radical gastrectomy in patients with stage E11 disease has 5- and 10-yr survival rates of 90% and 70%, respectively (81). However, radical gastrectomy can lead to significant morbidity and is therefore not optimal treatment in many patients. Endoscopic mucosal resection has been used as a curative method in patients unable or unwilling to undergo a radical gastrectomy (46). Radiation therapy has also shown promising results in stage E11 tumors. One study showed 100% complete remission of MALT lymphoma at a median follow-up time of 27 months with radiation alone (82). On the other hand, surgery and radiation in combination have also been used with similarly impressive results (83). More recently, monochemotherapy with alkylating agents such as chlorambucil or cyclophosphamide has been successfully used in patients who have failed *H. pylori* eradication alone (84). Levy *et al.* treated stage E11 patients not responding to *H. pylori* eradication with chlorambucil 6 mg/m², 14 days/month *p.o.* for 1 yr. They found that 58% of patients who did not respond to *H. pylori* eradication were in complete remission at a mean time of 7 months (70). In this study, the use of chlorambucil as adjuvant therapy in patients responding to *H. pylori* eradication was not beneficial.

The treatment of MALT lymphomas that present at advanced stages remains controversial. Surgery, radiation, and chemotherapy have all been used in the treatment of advanced disease, with less than optimal results. Surgery is useful for the removal of grossly visible lesions; however, radical gastrectomy has at best a 5-yr survival of 63% in stage E12 (81). Therefore, gastrectomy alone is not advocated for disease staged above E11 at presentation. Recent studies have advocated combined adjunctive radiation and surgery for stage E12 or E11 primary low grade gastric lymphomas with the addition of chemotherapy for high grade disease (81). Last, chemotherapy using the "CHOP" regimen (cyclophosphamide, hydroxydamnomyacin, Oncovin, and prednisone) should always be used in patients with end stage EIII and EIV disease if other treatment modalities are no longer an option. Rituximab, an anti-CD20 antibody, is currently undergoing investigation as a monochemotherapy in relapsing tumors (85). *H. pylori* eradication therapy should also be given in *H. pylori*-positive patients in addition to the above treatment, although its usefulness in advanced disease is still questioned.

FOLLOW-UP

Follow-up is essential in patients with MALToma treated with *H. pylori* eradication. Endoscopic findings alone are generally not useful for follow-up; however, an area of whitish or discolored mucosa with a granular pattern may be an endoscopic marker for regression of MALT lymphoma (86, 87). In addition, EUS has proven to be a useful modality for follow-up. The gastric wall may remain thick on EUS even if histology is negative. In this instance, multiple biopsies are needed to exclude persistent or relapsing tumor (88). Reinfection with *H. pylori* may lead to recurrence of the tumor, and monitoring of *H. pylori* status is necessary as well. Therefore, careful clinical and endoscopic follow-up, with multiple gastric biopsies for *H. pylori*, histological studies, and EUS at least yearly after remission is confirmed is essential (69, 70). Recurrences of MALToma have occurred years later, both locally and at distant sites, so follow-up should be indefinite (69, 70, 74).

It is likely that despite clinical and histological remission, some residual tumor cells lie dormant. Follow-up with biopsies taken for molecular studies has been debated. Molecular regression often lags behind histological regression by 1–2 yr. Monoclonal bands were reported to persist in almost 55% of cases, despite histological evidence of regression (86). It is unclear whether persistent monoclonality indicates the presence of residual disease. One study followed 11 histologically cured patients with persistence of monoclonality. All 11 patients had a sustained histological regression at 37 months (88). Consequently, molecular analysis by PCR did not help in determination of cure. Follow-up studies are needed to answer whether monoclonality places patients at a higher risk for relapse and if so, when screening should be initiated. In the meantime, the current gold standard is histological regression.

MALTOMA OR EXTRAMEDULLARY PLASMACYTOMA?

MALT lymphomas are histologically characterized by lymphoepithelial lesions composed of centrocyte- or centroblast-like cells. However, up to one third of all MALTomas reveal a plasma cell differentiation as well. This latter fact has been the focus of controversy in recent years, because extramedullary plasmacytomas can be found within the GI tract and are often difficult to distinguish from MALT lymphomas.

Plasmacytomas represent only 10% of all plasma cell neoplasms and are usually found within the bone marrow of patients with documented multiple myeloma. However, up to 20% of plasmacytomas may occur alone without bone involvement, and of those, up to 10% occur in the GI tract (89–91). Since the 1920s, GI plasmacytomas, have been repeatedly documented in the literature (92). MALTomas have been difficult to distinguish from GI plasmacytomas. Factors that suggest that the lesion represents a MALToma include a predominance of centrocyte- or centroblast-like

cells, characteristic lymphoepithelial lesions and CD20 expression. Factors that suggest a plasmacytoma include a predominance of plasma cells, presence of monoclonal immunoglobulins detected by immunoelectrophoresis, and tumors with a predominance of plasma cells containing monoclonal IgG or IgA chains (93). There has been a recent report of a plasmacytoma that may have differentiated from a MALT lymphoma, further emphasizing the close relationship between these two lesions (94).

Therapy of these two lesions differs considerably. As mentioned previously, the treatment of low grade, early stage MALTomas revolves around *H. pylori* eradication. On the other hand, extramedullary plasmacytomas are known to be extremely radiosensitive, with complete remission rates of up to 95% (89, 95–97). In addition, plasmacytomas are not known to respond to *H. pylori* eradication. Interestingly, another condition, called immunoproliferative small intestinal disease, appears to be a mix between MALTomas and plasmacytomas. This tumor is found in the proximal small intestine and contains a lymphoplasmacytic infiltrate that in two thirds of cases secretes an α -heavy chain protein (98). These tumors respond to tetracycline, although *H. pylori* eradication has also proved beneficial (99). Future studies are needed to investigate not only the potential relationship between these tumors but alternative therapies that are effective in tumors that contain features of both MALT lymphomas and plasmacytomas.

CONCLUSION

Gastric MALT lymphoma is a rare malignancy of the stomach. Its pathogenesis stems from the robust immunological reaction by a host infected with *H. pylori*. Patients who develop this tumor have a variety of vague complaints, making early diagnosis problematic. EUS and endoscopy with multiple tissue biopsies analyzed by rigid histopathological criteria are crucial for diagnosis. Once MALT lymphoma is found, treatment revolves around complete *H. pylori* eradication. Debate continues as to the treatment of patients who are either not *H. pylori* positive or who present at more advanced stages. In these subsets of patients, alternative treatment modalities should be investigated to improve the overall survival in people with this rare tumor.

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