

Gastric low-grade mucosal-associated lymphoid tissue-lymphoma: *Helicobacter pylori* and beyond

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Abstract

The stomach is the most frequently involved site for extranodal lymphomas, accounting for nearly two-thirds of all gastrointestinal cases. It is widely accepted that gastric B-cell, low-grade mucosal-associated lymphoid tissue (MALT)-lymphoma is caused by *Helicobacter pylori* (*H. pylori*) infection. MALT-lymphomas may engender different clinical and endoscopic patterns. Often, diagnosis is confirmed in patients with only vague dyspeptic symptoms and without macroscopic lesions on gastric mucosa. *H. pylori* eradication leads to lymphoma remission in a large number of patients when treatment occurs at an early stage (I-II₁). Neoplasia confined to the submucosa, localized in the antral region of the stomach, and without *API2-MALT1* translocation, shows a high probability of remission following *H. pylori* eradication. When both bacterial infection and lymphoma recur, further eradication therapy is generally effective. Radiotherapy, chemotherapy and, in selected cases, surgery are the available therapeutic options with a high success rate for those patients who fail to achieve remission, while data on immunotherapy with monoclonal antibodies (rituximab) are still scarce. The 5-year survival rate is

higher than 90%, but careful, long-term follow-up is required in these patients since lymphoma recurrence has been reported in some cases.

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Key words: Mucosal-associated lymphoid tissue; Therapy; *Helicobacter pylori*; Gastric lymphoma; Predictive factors; Endoscopy; Clinical presentation

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INTRODUCTION

Extranodal lymphomas account for 24%-29% of all the lymphomas in the USA and Taiwan, 36%-41% in Israel and the Netherlands, and 48% in Italy^[1]. The gastrointestinal tract is the most frequent site of extranodal lymphoma, and the stomach is involved in up to two-thirds of these cases, accounting for 30%-45% of all extranodal lymphoma^[2]. Although primary gastric lymphoma remains a rare disease, representing nearly 2%-8% of all tumors of the stomach, there is evidence that its incidence has been increasing in previous decades, similarly to lymphomas of the central nervous system and skin^[1]. In particular, a study performed in a Japanese tertiary center found that gastric lymphoma

was diagnosed in 15 patients in the period 1963-1967 and in 70 patients in the period 1998-2002, with percentages increasing from 32% and 26% in periods 1963-1982 and 1983-1992, respectively, to 43% in the period 1993-2002, clearly showing an increasing trend^[3]. Moreover, there are some geographic areas, such as north-eastern Italy, where the frequency of primary gastric lymphoma is particularly high, with an incidence as high as 13.2 cases per 100000 per year, which is significantly higher than that of other European countries^[4]. In 1991, the first study documenting the presence of *Helicobacter pylori* (*H. pylori*) infection in virtually all study cases of primary, low-grade, B-cell mucosal-associated lymphoid tissue (MALT)-lymphoma of the stomach was reported^[5]. Two years later, the first study reporting complete histological remission of gastric MALT-lymphoma in 5 of 6 patients following *H. pylori* eradication was published^[6], starting a new era in the management of patients with low-grade lymphoma of the stomach.

HOW DOES GASTRIC LYMPHOMA ARISE?

Although some aspects still remain unclear, the pathogenetic cascade of gastric lymphoma has been revealed. Structured lymphatic tissue; i.e. lymphatic follicles, is lacking in normal gastric mucosa. Indeed, through the alimentary tract, lymphatic tissue is exclusively present in tonsils and Peyer's patches. However, following inflammatory processes, lymphatic follicles may appear on gastric mucosa, configuring the so-called MALT, as described by Wright in 1983^[7]. Ten years later, Genta *et al*^[8] clearly showed that the main cause of MALT onset on gastric mucosa was *H. pylori*-related gastritis. In fact, when an adequate biopsy sampling (8-11 specimens) was performed, it was possible to document the presence of lymphatic follicles (from 1 to 20) in all infected patients, while none of the uninfected patients showed MALT. In addition, the study found that 1 year following *H. pylori* eradication, the number of lymphatic follicles was significantly reduced (from 6.6 to 2.2)^[8]. The presence of MALT in gastric mucosa could virtually be considered as a typical sign of *H. pylori* infection and, consequently, each infected patient is potentially at risk of developing gastric MALT-lymphoma during a life-long infection. However, based on the high prevalence of *H. pylori* infection in the general population, on the one hand, and the low incidence of gastric lymphoma, on the other, it is arguable that some particular conditions are needed for the neoplasia to develop. In an experimental study that involved co-culturing lymphocytes isolated from 3 gastric MALT-lymphoma and various inactivated *H. pylori* strains, a proliferation of B cells that also expressed IL-2 receptors was observed and a simultaneous IL-2 production by T cells in supernatant was detected^[9]. Of note, only 1 of the 13 different *H. pylori* strains tested was able to stimulate B lymphocyte proliferation, and the involved bacterial strain was different among the 3 studied lymphoma patients. Moreover, T cell removal from the

culture markedly reduced *H. pylori*-induced proliferation of B cells, suggesting an interaction between bacteria and T helper lymphocytes^[9]. In addition, no B cell proliferation was observed when incubating gastric lymphoma cells with either *E. coli* or *C. jejuni*, suggesting a specific role for *H. pylori*. Moreover, *H. pylori* were unable to stimulate B cells of either thyroid- or salivary-derived lymphoma^[9]. The latter observation is particularly worthy of attention, since lymphoma onset following a chronic inflammatory process on either thyroid (autoimmune thyroiditis) or salivary glands (Sjögren syndrome) has been clearly recognized^[10,11].

On the other hand, certain genetic predispositions to gastric lymphoma onset have been highlighted. Noteworthy, a significantly higher prevalence of both HLA-DQA1*0103 and HLA-DQB1*0601 alleles and of DQA1*0103-DQB1*0601 haplotypes has been observed in MALT lymphoma patients as compared to controls with or without *H. pylori*-infection^[12]. In addition, the R702W mutation in the NOD2/CARD15 gene was significantly associated with gastric lymphoma, and those subjects with the rare allele T had an increased risk (OR = 2.4, 95% CI: 1.2-4.6) to develop lymphoma compared to controls^[13]. Similarly, the TNF-857 T allele was found in 15.1% of patients with low-grade lymphoma and 9.1% of controls (OR = 1.8, 95% CI: 1.1-2.8)^[14]. The rare allele G of Toll-like receptor 4 (TLR4 Asp299Gly) appeared to be one putative factor in the genetic susceptibility to gastric lymphoma^[15]. On the contrary, homozygous haplotypes for the rare allele G of SNP3 (rs12969413) of the *MALT1* gene significantly protected patients from high- but not from low-grade gastric lymphoma^[16].

In summary, these observations clearly demonstrate that only some *H. pylori* strains in some predisposed patients determine lymphoma development in the stomach, according to a strain-host-organ specific process^[17].

WHAT IS THE CLINICAL-ENDOSCOPIC LYMPHOMA PRESENTATION?

H. pylori infection induces a B-cell, low-grade, gastric MALT-lymphoma, typically CD19+, CD20+, usually CD5-, always CD10- and CD23-, with a clinically indolent progression^[18]. Indeed, the neoplasia remains confined in the gastric mucosa for a long-time, so that its real tumoral nature has been questioned in the past when it was interpreted as "pseudo-lymphoma"^[19]. Successive studies documented the monoclonal feature of B cells and the presence of a number of genetic alterations in these cells, such as trisomy 3, *API2-MALT1* translocation, *p53* mutation, and *p16* deletion^[18,19]. Moreover, neoplastic B cells show aggressive behaviour causing the so-called lymphoepithelial lesions, which are a pathognomonic sign of lymphoma, by invading and destroying gastric glands. In addition, lymphoma cells are able to invade the entire gastric wall, from the mucosa to the serosa, and have the potential of metastasizing in both lymph nodes and other organs, particularly the bone marrow, lungs and liver^[18-20].

Table 1 Endoscopic presentation of primary gastric MALT-lymphoma

Type	Main endoscopic presentation
Ulcerative	Single or multiple ulcerations or multiple erosions
Exophytic	Tumor-like appearance with an irregular or polypoid mass
Hypertrophic	Large or giant folds; nodular pattern
Mixed	A combination of more than one pattern
Petechial	Presence of several mucosal petechial haemorrhages
Normal/hyperaemic	Normal appearing mucosa/hyperaemic changes

MALT: Mucosal-associated lymphoid tissue.

Therefore, the tumoral nature of MALT-lymphoma of the stomach has been definitely demonstrated. From a clinical point of view, gastric MALT lymphoma occurs over a wide age range, with a median of 57 years^[18,21]. Although the sex ratio incidence is essentially equal, neoplasia appears to be slightly more prevalent in males (male:female = 1.27:1)^[21]. Frequently, only vague dyspeptic symptoms are present, and B symptoms are extremely rare in MALT-lymphoma of the stomach, so that the diagnosis is often incidental^[19]. In other cases, neoplasia may present as a complication of the gastric lesion, such as gastrointestinal bleeding or perforation. Persistent vomiting and weight loss are other possible presenting symptoms. Similarly, at endoscopic observation, MALT-lymphoma may present with different macroscopic features, from a normal appearing gastric mucosa to an ulcerative or vegetant mass, clearly suggesting a malignancy.

In a recent systematic review, clinical and endoscopic presentation of gastric lymphoma has been assessed considering data from 2000 patients^[21]. By classifying the presenting symptoms as “alarm” (anaemia and/or melaena and/or haematemesis, persistent vomiting, weight loss) or “not alarm” (epigastric and/or abdominal pain, dyspepsia and/or bloating, heartburn), according to the current international guidelines^[22,23], we found that alarm symptoms were present in only 42.1% of low-grade lymphoma patients^[21]. The relatively low prevalence of alarm symptoms seems to be different from that observed in gastric or oesophageal cancer patients, in whom these symptoms are present in 56%-62% of cases^[24]. Despite the indolent behaviour of low-grade gastric lymphoma, we computed that neoplasia was diagnosed in an advanced stage (III-IV) in as many as 9.4% of the cases^[21]. Such an observation presumably depends on the absence of alarm symptoms in the majority of cases, prompting both patients and physicians to undertake an upper endoscopy.

As for the presenting endoscopic feature, we have recently proposed a modified classification (Table 1)^[21], updating the classification previously proposed by Ahmad *et al.*^[25] Using this updated classification, the neoplasia appeared as an ulcerative type in 52.1%, hypertrophic in 23.5%, normal/hyperaemic in 12.7%, exophytic in 9.7%, and as petechial pattern in 1% of cases among 1055 low-grade MALT-lymphoma patients^[21]. Of note,

Table 2 Gastric lymphoma staging

Ann Arbor	TNM	Description
I	T1-T4 N0 M0	Confined within the gastric wall
II ₁	T1-T4 N1 M0	Perigastric lymph nodes
II ₂	T1-T4 N2 M0	Regional lymph nodes
III	T1-T4 N3 M0	Lymph nodes on both sides of the diaphragm
IV	T1-T4 N0-3 M1	Visceral metastasis or second extranodal site

these data showed that, in nearly 15% of cases, such a neoplasia may be detected on normal appearing mucosa or in the presence of solely petechial haemorrhages; that is, endoscopic features suggesting a benign condition.

HOW TO TREAT LOW-GRADE GASTRIC LYMPHOMA?

The discovery of the etiologic role of *H. pylori* infection in gastric low-grade, B-cell MALT-lymphoma has radically changed the therapeutic approach for such neoplasia. Moreover, recent studies suggest that this infection plays a relevant role even in high-grade, large B cell lymphoma of the stomach, although data are still limited^[26]. Current international guidelines suggest *H. pylori* eradication as first-line therapy in all low-grade gastric lymphoma patients when neoplasia is diagnosed at an early stage^[22,23,27], according to the modified Ann Arbor classification (Table 2). Therefore, a comprehensive staging procedure, with a complete physical examination including Waldeyer's ring, routine laboratory tests, chest radiograph, endoscopic ultrasonography, computed tomography of the abdomen and pelvis, as well as bone marrow biopsy is mandatory in all gastric lymphoma patients. Indeed, bone involvement (stage IV) has been reported in up to 15% of cases, requiring oncologic therapy^[19,28]. In a very large, pooled data analysis on patients with gastric lymphoma and *H. pylori*, it has been found that after first-line eradication therapy, the infection was cured in 91% of cases, with the success rate being higher following dual therapy as compared to the 7-day or 14-day triple therapies^[29]. After second-line therapy, the eradication rate was 80.8%, being higher following triple rather than quadruple therapy. Further therapies (from three to five attempts) cured the infection in 75% of patients, so that *H. pylori* infection was ultimately cured in 99.8% of cases^[29]. Another study found that lymphoma remission was achieved in 77.5% of 1408 patients with low-grade lymphoma at an early stage (I - II₁) following successful bacterial eradication with a median time of 5 mo^[30]. Interestingly, different predictive factors for lymphoma remission were identified, including neoplasia stage, depth of infiltration in the gastric wall, localization in the stomach, patient ethnicity, and presence of the *API2-MALT1* translocation. Indeed, neoplasia remission was higher in stage I than in stage II₁ (78.4% *vs* 55.6%; *P* = 0.0003), as well as when it was confined to the submucosa as compared to a deeper invasion (82.2% *vs* 54.5%; *P* = 0.0001), when it was localized to the distal rather than in the proximal stomach (91.8% *vs* 75.7%; *P* = 0.0037), and in

Asian rather than in Western patients (84.1% *vs* 73.8%; $P = 0.0001$)^[30]. Moreover, the remission rate was higher among patients without the *API2-MALT1* translocation (78% *vs* 22.2%; $P = 0.0001$)^[30], a mutation which impairs the control of cell apoptosis, disconnecting the proliferation process by the bacterial antigenic stimulus^[18]. Several long-term follow-up trials showed that the overall 5-year survival (OS) and disease-free survival (DFS) rates were as high as 90% and 75%, respectively, when lymphoma was treated in an early stage^[31]. In a multicenter, Italian study, we calculated an OS of 94.7% and a DFS of 74.6% based on 60 patients with a mean follow-up of 65 mo^[28].

HOW TO TREAT NOT RESPONDING LYMPHOMA PATIENTS?

Although specific guidelines on the management of lymphoma patients who failed to achieve neoplasia remission following *H. pylori* eradication are lacking, the European Society of Medical Oncology recommend the use of conventional anti-neoplastic therapeutic approaches^[32]. In detail, either chemotherapy or radiotherapy is suggested as first-line oncologic treatment, while surgery should be reserved for selected cases. Recently, the possible role of immunotherapy with rituximab, which is an anti-CD20 monoclonal antibody, has been investigated, but data are still limited^[33]. Considering the results of 27 trials enrolling 280 patients with early stage neoplasia who failed to respond to *H. pylori* eradication therapy, it has been found that lymphoma remission was achieved overall in 92.8% of patients treated with an oncologic therapy^[34]. In particular, the remission rate following radiotherapy was higher than that of chemotherapy (97.8% *vs* 85.9%; $P = 0.01$), and was similar to that of surgery. However, radiotherapy preserves the stomach and its functions, without the possible long-term complications of gastric surgery, which include cancer risk on the remnant stomach. On the contrary, data on rituximab monotherapy seem to be less encouraging, with the lymphoma remission rate being achieved in only 59.3% of 27 treated patients^[34]. Overall, these data suggest that it is possible to successfully treat more than 90% of patients who fail lymphoma remission following *H. pylori* eradication.

HOW TO PERFORM THE FOLLOW-UP?

Since neoplasia recurrence is possible even years following a complete histological remission, patients with gastric lymphoma need long-term follow-up. In an analysis of results from 994 patients, 7.2% experienced lymphoma relapse during 3253 patient-years of follow-up, with a yearly recurrence rate of 2.2%^[30]. Lymphoma relapse in these patients may occur either following *H. pylori* reinfection or without infection recurrence. A systematic review found a bacterial reinfection in 18 (2.7%) of 676 gastric lymphoma patients at long-term follow-up, with an estimated yearly reinfection rate of 0.7%^[29]. Therefore, a scheduled histological follow-up is mandatory in these

patients in order to promptly detect either a bacterial recurrence or lymphoma relapse.

Based on both the possible multifocal involvement of the gastric mucosa and the absence of clear endoscopic lesions in some patients, lymphoma remission should be regarded as achieved only when consecutive controls have been negative. In particular, following *H. pylori* therapy, as well as an anti-neoplastic therapy, at least 2 consecutive (at 1 and 3 mo) negative endoscopic and histological controls are recommended to correctly establish neoplasia remission^[32]. When remission is achieved, further endoscopic controls, with biopsy mapping on all the gastric sites, should be performed every 6 mo for the first 2 years and every 12 mo for the successive 5 years (Table 2), even though there are no clear recommendations for the end of follow up^[32]. In some patients, minimal lymphoma residuals may persist at histological assessment without macroscopic lesions detectable at endoscopy. It has been suggested that these patients may be safely managed with a “watch and wait” strategy based on scheduled follow-up. Indeed, a recent study enrolling 107 stage I lymphoma patients with a median follow-up of 42.2 mo found that histological residuals regressed in 32% cases without any further therapy, remained stable in 67%, progressed in 4%, while one patient developed high-grade lymphoma^[35]. The possibility of onset of a high-grade neoplasia has been also determined in a pooled-data analysis where 0.05% of patients who were initially cured for low-grade lymphoma developed a high-grade neoplasia at long-term follow-up^[30]. Another possible consequence following successful remission of gastric lymphoma is represented by the onset of a second neoplasia^[28,36]. Indeed, a study found that as many as 9 of 10 deaths were due to a cancer development within 3 years following lymphoma remission^[37]. In particular, an increased incidence of gastric cancer has been observed in these patients^[31,38]. These observations suggest that patients with gastric lymphoma require an extensive follow up, not only for possible lymphoma recurrence in the stomach, but also for an increased neoplastic risk, which seems only in part to be related to the use of chemotherapy^[19,39].

CONCLUSION

The stomach is the most frequently involved site for extranodal lymphoma. Among gastric lymphomas, the onset of a low-grade, B-cell neoplasia is strictly linked to *H. pylori* infection, according to a strain-host organ-specific process^[9]. A definitive role for *H. pylori* in high-grade transformed MALT lymphoma has been also recently highlighted^[26], and remission of low-grade lymphoma with antibiotic therapy has been anecdotally reported in some patients with undetectable *H. pylori* infection^[40]. Primary gastric lymphoma shows an overall good prognosis when diagnosed and treated at an early stage; that is, when it is confined to the gastric wall or local lymph nodes. Indeed, *H. pylori* eradication leads to lymphoma remission in nearly 80% of stage I patients and in more than half

of the cases when neoplasia is treated in stage II. When neoplastic lesions are confined within the sub-mucosa, localized in the antral region of the stomach, or the *AP12-MALT1* translocation is lacking in the tumoral B cells, lymphoma remission is highly probable following *H. pylori* eradication^[30]. In those patients with lymphoma persistence despite bacterial cure, anti-neoplastic therapy is needed, and radiotherapy seems to be the most effective treatment^[34]. Immunotherapy with monoclonal antibodies is an emerging therapeutic strategy and its role, particularly as a concomitant therapy, deserves to be evaluated in future trials. It has been recommended that surgery should be reserved for select cases, since equally effective and stomach-conserving therapies are available^[32]. When lymphoma remission has been opportunely verified, a scheduled long-term endoscopic, histological follow up is needed in all gastric lymphoma patients. Finally, the higher probability of a second neoplasia in these patients requires careful clinical control.

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