

Gastric MALT lymphoma: old and new insights

Angelo Zullo^a, Cesare Hassan^a, Lorenzo Ridola^a, Alessandro Repici^b, Raffaele Manta^c,
Alessandro Andriani^d

Nuovo Regina Margherita' Hospital, Rome; IRCCS Istituto Clinico Humanitas, Milan; New S. Agostino Hospital, Modena, Italy

Abstract

The stomach is the most frequent site of extranodal lymphoma. Gastric lymphoma originating from mucosa-associated lymphoid tissue (MALT) is typically a low-grade, B-cell neoplasia strongly associated with *Helicobacter pylori* (*H. pylori*) infection. Only certain *H. pylori* strains in some predisposed patients determine lymphoma development in the stomach, according to a strain-host-organ specific process. The clinical presentation is poorly specific, symptoms ranging from vague dyspepsia to alarm symptoms. Similarly, different endoscopy patterns have been described for gastric lymphoma. *H. pylori* eradication is advised as first-line therapy in early stage disease, and complete lymphoma remission is achieved in 75% of cases. Neoplasia stage, depth of infiltration in the gastric wall, presence of the *API2-MALT1* translocation, localization in the stomach, and patient ethnicity have been identified as predictors of remission. Recent data suggests that *H. pylori* eradication therapy may be successful for gastric lymphoma treatment also in a small subgroup (15%) of *H. pylori*-negative patients. The overall 5-year survival and disease-free survival rates are as high as 90% and 75%, respectively. Management of patients who failed to achieve lymphoma remission following *H. pylori* eradication include radiotherapy, chemotherapy and, in selected cases, surgery.

Keywords *Helicobacter pylori*, MALT lymphoma, gastric lymphoma, eradication therapy, anti-tumor therapy

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Epidemiology

Although lymphomas mainly involve lymph nodes, spleen, and bone marrow, extranodal non-Hodgkin's lymphomas (NHL) account for 24-29% of all the lymphomas in the USA, Canada and Taiwan, 36-44% in Israel, Denmark, the Netherlands, and Lebanon, 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. Indeed, 30-45% of all extranodal lymphomas are detected in the stomach [2]. While its frequency is rising in the last decades, primary gastric lymphoma remains a rare disease,

representing nearly 2-8% of all tumors of the stomach [1,3]. 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 100,000 per year, which is significantly higher than that of other European countries [4].

Pathogenesis

Virtually all gastric lymphomas arise from B-cell [2]; T-cell neoplasia of stomach is extremely rare [5]. They include marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), which account for nearly 50% of gastric lymphomas, and diffuse large B-cell lymphomas (DLBCL), whilst both follicular and mantle cell lymphomas are infrequent [5,6]. The marginal zone lymphoma – usually named MALT lymphoma – is typically a low-grade neoplasia, characterized by a dense lymphoid infiltrate mainly composed of small-size lymphocytes that invade and destroy gastric glands, configuring the so-called 'lymphoepithelial lesion' which is pathognomonic of lymphoma [7]. Although a specific antigenic profile of MALT lymphomas does not exist, the B-cells sharing the immunophenotype with marginal zone B-cells present in the spleen, Peyer's patches and lymph nodes, gastric lymphoma is

^aGastroenterology and Digestive Endoscopy, 'Nuovo Regina Margherita' Hospital, Rome (Angelo Zullo, Cesare Hassan, Lorenzo Ridola); ^bDepartment of Gastroenterology, IRCCS Istituto Clinico Humanitas, Milan (Alessandro Repici); ^cGastroenterology and Endoscopy Unit, New S. Agostino Hospital, Modena (Raffaele Manta); ^dOnco-Hematology Unit, 'Nuovo Regina Margherita' Hospital, Rome (Alessandro Andriani), Italy

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Correspondence to: Dr. Angelo Zullo, Ospedale Nuovo Regina Margherita, Gastroenterologia ed Endoscopia Digestiva, Via Emilio Morosini, 30, 00153 Rome, Italy, e-mail: zullo66@yahoo.it

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CD20⁺, CD5⁺, CD10⁻, CD23⁻, and cyclin D1⁻ [8]. Low-grade MALT lymphoma of the stomach is strongly associated with *H. pylori* infection. The DLBCL is a high-grade lymphoma in which the role of *H. pylori* is still controversial, although data are accumulating [9]. The possibility of transformation from low- to high-grade lymphoma motivated a classification suggesting a continuum from a very low-grade to pure high-grade lymphoma, including two intermediate stages based on the presence of a number of immunoblast cells (Table 1) [10].

The pathogenetic cascade of gastric lymphoma has been for the most part discovered. Although lymphatic follicles are lacking in normal gastric mucosa, they may appear following an inflammatory process, configuring the so-called MALT [7]. It has been demonstrated that *H. pylori*-related gastritis is the main cause of MALT onset on gastric mucosa [11]. Indeed, development of MALT in gastric mucosa may be considered a pathognomonic sign of *H. pylori* infection. Consequently, each infected patient is at potential risk of developing gastric MALT lymphoma during a lifelong infection. However, based on the very 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 neoplasia development. Some experimental observations have elucidated the mainstream process involved. By co-culturing lymphocytes isolated from gastric MALT-lymphoma patients and various inactivated *H. pylori* strains, a proliferation of B-cell expressing IL-2 receptors was observed, and IL-2 production by T cells in supernatant was also detected [12]. It is noteworthy that only 1 of the 13 different *H. pylori* strains tested was able to stimulate B-cell proliferation, and the bacterial strain involved changed among the 3 studied lymphoma patients. In addition, *H. pylori*-induced B-cell proliferation was markedly reduced when T cells were removed from the culture, suggesting an interaction between bacteria and T-helper lymphocytes. Moreover, both *Escherichia coli* and *Campylobacter jejuni* – i.e. Gram negative intestinal bacteria which share different antigens with *H. pylori* – failed to induce B-cell proliferation in culture, clearly indicating a specific role for *H. pylori* strains. On the other hand, *H. pylori* was unable to stimulate B cells of either

thyroid- or salivary-derived lymphomas [12]. Further studies elucidated the role of other cytokines involved in B-cell activation during gastric lymphomagenesis. In detail, gastric MALT lymphoma express high levels of a proliferation inducing ligand (APRIL), a novel cytokine crucial in sustaining B-cell proliferation [13]. It has been recently found that APRIL is produced by gastric lymphoma infiltrating macrophages located in close proximity to neoplastic B cells [14]. Of note, APRIL production by macrophages was induced by *H. pylori* and *H. pylori*-specific T cells [14].

Differently from gastric cancer and peptic ulcer disease, virulent factors of *H. pylori* seem to play a marginal role in the pathogenesis of gastric lymphoma [15]. However, the prevalence of CagA positive strains was found to be significantly higher in DBCL than in low-grade MALT lymphoma [16]. In addition, a recent study demonstrated that *H. pylori* may translocate CagA protein directly into B cells where it induces extracellular signal-regulated kinase activation and Bcl-2 expression up-regulation resulting in apoptosis inhibition [17]. It has been also observed that gastric lymphoma patients infected with CagA positive *H. pylori* strains responded to eradication therapy significantly quicker than those without [18].

Some genetic alterations involved in the transformation from normal B cells to malignant clone during *H. pylori* infection have been observed [19,20]. Three chromosomal translocations – t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21) are the most frequently detected. They are involved in the same signaling pathway, resulting in activation of nuclear factor kappa B (NF-κB), which plays a role in immunity, inflammation, and apoptosis [21, 22]. In detail, the t(11;18)(q21;q21) – found in approximately one third of cases and is often the only cytogenetic alteration [23] – causes the fusion of cellular inhibitor of apoptosis protein 2 (API2) on 11q21 with the MALT1 on 18q21. The *API2-MALT1* fusion encodes for an aberrant protein which is lacking apoptotic effect towards B cells that, consequently, may proceed to a monoclonal expansion [24]. Of note, it has been found that the prevalence of CagA-positive *H. pylori* strains was significantly higher in gastric MALT-lymphoma patients with the t(11;18)(q21;q21) compared to those without such a translocation (93.3% vs. 51.9%; P=0.01) [25].

On the other hand, a familial background of NHL has been highlighted [26,27]. Basically, the overall NHL risk for a person with a first-degree relative compared to a stratified control collective was reported at an odds ratio (OR) of 1.5 [26]. A role for a genetic predisposition in gastric lymphoma development has also been pointed out. Indeed, the prevalence *HLADQA1*0103* and *HLA-DQB1*0601* alleles and of *DQA1*0103-DQB1*0601* haplotypes was found to be increased in MALT-lymphoma patients as compared to controls [28]. Moreover, the presence of the R702W mutation in the *NOD2/CARD15* gene significantly increases the risk of gastric lymphoma development, particularly when the rare allele T was present (OR 2.4, 95% CI 1.2-4.6) [29]. Likewise, the presence of *TNF-857 T* allele was associated with a higher risk of low-grade gastric lymphoma (OR 1.8, 95% CI 1.1-2.8) [30]. In addition,

Table 1 Histological classification of gastric MALT-lymphoma based on presence of blast clusters and diffuse blastic component (modified from reference 10)

Lymphoma sub-group	Cluster size	Diffuse blast component*	Grade
A (pure low-grade)	<5	<1%	Low-grade
B (low-grade with high-grade component)	5-20	<10%	
C (high-grade with low-grade component)	>20	>10%	High-grade
D (pure high-grade)	>20	>10%	

*Blasts were defined as large tumor cells with one or more nucleoli and a vesicular or coarse chromatin pattern

the rare allele G of Toll-like receptor 4 (*TLR4 Asp299Gly*) appeared to be one putative factor in the genetic susceptibility to gastric lymphoma [31]. 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 [32].

Summarizing all these observations, it may be concluded that only certain *H. pylori* strains in some genetically predisposed patients determine lymphoma development in the stomach, through a strain-host-organ specific process.

Clinical-endoscopic presentation

Gastric MALT lymphoma in most cases behaves as an indolent disease. The clinical presentation of gastric lymphoma is poorly specific, symptoms ranging from vague dyspepsia, including epigastric pain or discomfort centered in the upper abdomen to, less frequently, alarm symptoms, such as gastrointestinal bleeding or persistent vomiting [5]. Classic B symptoms (fever, night sweats, weight loss) are extremely rare in MALT lymphoma of the stomach. A recent systematic review including data of 2,000 patients found that gastric MALT lymphoma occurs over a wide age range, with a mean of 57 years [33]. Although the sex ratio incidence is essentially equal, gastric lymphoma appears to be slightly more prevalent in males (male:female 1.27:1). Of note, alarm symptoms were present in only 42.1% of low-grade lymphoma patients. Therefore, a gastric MALT lymphoma is sometimes diagnosed following an upper endoscopy performed for vague dyspeptic symptoms.

Similarly, different, nonspecific endoscopy patterns have been described for gastric lymphoma. Although it may appear at endoscopy as a clear malignant lesion (giant ulcer, vegetant mass, etc.), it is frequently characterized simply by erosions, small nodules, thickening of gastric folds – generally suggesting a benign condition – or even by apparently normal gastric mucosa. Based on these observations, an updated endoscopic classification has been proposed (Table 2) [34]. By using this classification, the neoplasia appeared as an ulcerative type in

52.1%, hypertrophic in 23.5%, normal/hyperemic in 12.7%, exophytic in 9.7%, and as a petechial pattern in 1% of cases among 1055 low-grade MALT-lymphoma patients [33]. Therefore, such a neoplasia may be detected on normal appearing mucosa or in the presence of solely petechial hemorrhages in nearly 15% of cases. The actual role of magnifying endoscopy in improving endoscopic diagnosis of MALT-lymphoma based on detection of destructed gastric pits, irregular pit size and their distribution deserves further investigation [35].

Staging procedures

Although gastric MALT lymphoma has an indolent course with a low disease-related morbidity and mortality, an accurate staging procedure is mandatory in all diagnosed cases [36]. Indeed, it has been found that low-grade gastric lymphoma is diagnosed in an advanced stage (III-IV) in near 10% of the cases, with localization in both lymph nodes and other organs, particularly the bone marrow, lungs and liver [37]. Therefore, a comprehensive staging procedure, with a complete physical examination including Waldeyer's ring, routine laboratory tests (including lactate dehydrogenase and β 2-microglobulin), computed tomography of the chest, abdomen and pelvis, endoscopic ultrasonography, as well as bone marrow biopsy is mandatory in all gastric lymphoma patients. Indeed, bone marrow involvement (stage IV) has been reported in up to 15% of cases, requiring anti-neoplastic therapy [23].

The endoscopic ultrasound (EUS) allows to accurately assess both the infiltration of lymphoma in the gastric wall and the regional lymph nodes involvement [38-40]. Of note, the depth of invasion into the different layers of gastric wall is predictive of lymphoma remission following therapy [39]. The role of positron emission tomography scan in such a setting is still unclear [41].

Therapeutic management

H. pylori eradication therapy in infected patients

The discovery of the etiologic role of *H. pylori* infection in gastric lymphoma has radically changed the therapeutic approach for such neoplasia. Both current oncology and gastroenterology international guidelines advise *H. pylori* eradication as first-line therapy for early stage (I-II₁ according to the modified Ann Arbor classification), low-grade, MALT lymphoma; that is when the neoplasia is confined in the stomach or in perigastric lymph nodes [36,42,43]. Besides *H. pylori* eradication, patients diagnosed in a more advanced stage require adjunctive anti-tumor therapy.

A large pooled-data analysis found that first-line eradication treatment, with either a high-dose dual or 7-14 days triple therapies, cured *H. pylori* infection in 91% of cases [44]. After the second-line therapy, the overall eradication rate was

Table 2 Updated endoscopic classification of gastric MALT-lymphoma (modified from reference 34)

Endoscopic feature	Lymphoma type
Single/multiple ulcerations or erosions	Ulcerative
Irregular or polypoid mass	Exophytic
Large gastric fold/Nodular mucosa	Hypertrophic
Multiple mucosal petechial hemorrhage	Petechial hemorrhage
Absence of macroscopic lesions	Normal
A combination of more patterns	Mixed

80.8%, being higher following triple than quadruple regimen. Further therapies (from 3 to 5 attempts) cured the infection in 75% of patients, so that *H. pylori* infection was eventually cured in 99.8% of cases [44]. However, it should be noted that the eradication rate following standard triple therapies is decreasing in clinical practice, mainly due to an increased prevalence of primary antibiotic resistance in *H. pylori* isolates worldwide [45]. Therefore, it is like that more effective first-line regimens – such as sequential or concomitant therapy [46] – should be used also in gastric lymphoma patients.

Following successful bacterial eradication, lymphoma remission was achieved in 77.5% of 1,408 patients with low-grade lymphoma at an early stage with a median time of 5 months [47]. Interestingly, different predictive factors for lymphoma remission were identified, including neoplasia stage, depth of infiltration in the gastric wall, presence of the *API2-MALT1* translocation, localization in the stomach, and patient ethnicity. Indeed, neoplasia remission was higher in stage I than in stage II₁ (78.4% vs. 55.6%), when it was confined to the submucosa as compared to a deeper invasion (82.2% vs. 54.5%), when *API2-MALT1* translocation was absent (78% vs. 22.2%), when it was localized to the distal rather than in the proximal stomach (91.8% vs. 75.7%), and in Asian rather than in Western patients (84.1% vs. 73.8%) [47]. In addition, the infiltration of CD4+ FOXP3+ regulatory T (Treg) in gastric lymphoma may play a role in therapeutic response. Indeed, it has been recently observed that both the FOXP3+/CD4+ cell ratio and the absolute number of FOXP3+ cells were significantly greater in *H. pylori* eradication responders as compared with nonresponders [48,49]. On the contrary, the over-expression of either *miR-142-5p* (i.e. hematopoietic-specific microRNA) or *miR-155* (i.e. potential oncogenic microRNA) in MALT-lymphoma tissue was associated with a lower probability of response to *H. pylori* therapy [50].

Several long-term follow-up trials showed that the 5-year overall survival (OS) and disease-free survival (DFS) rates were as high as 90% and 75%, respectively, when lymphoma was treated at an early stage [51]. A study found that *HLA-DR* antigen and *PECAM-1* were statistically significant independent prognostic factors associated with favourable and unfavourable prognosis, respectively [52]. 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 successful 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 months) negative endoscopic and histological controls are recommended to correctly establish neoplasia remission [36,42]. When remission is achieved, further endoscopic controls, with biopsy mapping on all the gastric sites, should be performed every 6 months for the first 2 years and every 12 months for the successive 5 years, even though there are no clear recommendations for the end of follow up [36,42]. The EUS in the follow up of gastric lymphoma seems not to be a reliable tool, the concordance between such a method and histology being reported to be as low as 33% [53], and therefore histology still remains the gold standard [54].

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 [55]. Indeed, it has been found that histological residuals regressed or remained stable in the majority of patients and progressed in only 5% of cases.

Despite a complete histological remission, lymphoma recurrence is possible even after some years. Neoplasia recurrence essentially involves the stomach, and a lymph node relapse has been rarely described [56,57]. In an analysis of 994 patients, 7.2% experienced lymphoma relapse after 3,253 patient-years of follow up, with a yearly recurrence rate of 2.2% [47]. Moreover, 5 (0.05%) patients initially cured of both *H. pylori* infection and lymphoma developed high-grade lymphoma. Lymphoma relapse may occur either with or without *H. pylori* 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% in these patients [47].

Even though data are still limited, different studies suggest that *H. pylori* infection plays a relevant role even in the high-grade, DLBCL of the stomach. A systematic review found lymphoma remission in 42 (69%) out of 61 patients, following first-line antibiotic therapy for *H. pylori* infection [8]. Further prospective studies are warranted in such a setting to confirm these clinically relevant observations.

On the other hand, a recent case report described a complete remission of *H. pylori*-associated gastric MALT lymphoma diagnosed at stage IV (mediastinal lymph node involvement) by exclusively using eradication therapy [58]. This intriguing observation, if confirmed in large studies, may open a new, safer and cheaper therapeutic approach also for advanced stage gastric MALT-lymphoma patients.

***H. pylori* eradication therapy in uninfected patients**

An initial therapeutic attempt with *H. pylori* eradication therapy could be attempted even in *H. pylori* negative patients [36], as pointed out by the observation of complete lymphoma remission following eradication therapy in some uninfected patients [59,60]. A recent systematic review, including data of 11 studies with 110 patients with low-grade gastric lymphoma, showed that eradication therapy achieved complete lymphoma regression in 17 (15.5%; 95% CI 8.7-22.2) patients, although *H. pylori* infection was initially excluded with at least 3 different diagnostic tests [61]. As a possible interpretation of these data, it has been suggested either that *H. pylori* infection is present, despite the negative results of all the 3-5 diagnostic tests (i.e. false negative) or that antibiotic therapy may act against other bacteria potentially involved in MALT-lymphoma pathogenesis [61]. Anyway, these data confirm that eradication therapy may be successful for gastric lymphoma treatment also in a small subgroup of *H. pylori*-negative patients. Therefore, based on the generally indolent behavior of this neoplasia, a novel therapeutic algorithm has

been proposed recommending eradication therapy in all low-grade MALT-lymphoma patients, irrespective of *H. pylori* status, before resorting to aggressive, costly, and potentially more toxic oncologic therapies [61]. Indeed, with such an approach, the number needed to treat (NNT) to prevent a potentially useless oncologic therapy would be 67.

Treatment in unresponsive patients

Despite the fact that *H. pylori* eradication achieves a high lymphoma remission rate, the neoplasia may persist in nearly 20-25% of patients, requiring further therapeutic approaches. Although no specific guidelines on the management of these patients are available, the European Society of Medical Oncology recommends the use of conventional anti-neoplastic therapeutic approaches [42]. In detail, either chemotherapy or radiotherapy is suggested as first-line anti-tumor treatment, while surgery should be reserved for only selected cases. 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 anti-neoplastic therapy [62]. In particular, the remission rate following radiotherapy was higher than that of chemotherapy (97.8% vs. 85.9%), 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. A retrospective, multicenter study on 102 patients with a median follow up of 7.9 years, recently showed an 88% (95% CI 82-95) remission rate following radiotherapy, and presence of either large B-cell component (P=0.036) or exophytic growth pattern (P=0.042) were negative predictive factors of treatment failure [63]. In another retrospective study, 97.1% of 34 MALT-lymphoma patients unresponsive to *H. pylori* therapy achieved complete remission with radiotherapy, with a 5-year recurrence-free survival rate of 97% [64].

The potential therapeutic role of immunotherapy with rituximab, which is an anti-CD20 monoclonal antibody, has been investigated, but lymphoma remission was achieved in only 59.3% of 27 treated patients [65]. However, a recent randomized study [66], found that the addition of rituximab to chlorambucil therapy was significantly better than chlorambucil alone, with 95% (95% CI 88-98) and 86% (95% CI 77-92%) of patients in continuous remission at 2 years follow up, respectively. In addition, a significantly higher event-free survival (HR 0.52; 95% CI 0.34-0.79) at 5-year follow up was observed, whilst the OS rate was the same (89%) [66].

Some experimental data would suggest a potential role for vascular endothelial growth factor (VEGF) as a target therapy for MALT lymphoma. Indeed, by administering VEGF receptor antibodies or celecoxib, one of the cyclooxygenase 2 inhibitors, to *Helicobacter heilmannii*-induced gastric lymphoma mice, a significant decrease in the tumor size was observed [67]. Therefore, other therapeutic strategies could be available in the future.

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