Abstract

Mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent extranodal marginal zone B-cell lymphoma, originating in acquired MALT that is induced in mucosal barriers as part of a normal adaptive immune response to a chronic immunoinflammatory stimulus, most notably chronic infection by Helicobacter pylori (H. pylori). This antigenic stimulation initially leads to lymphoid hyperplasia; the acquisition of additional genetic aberrations culminates in the activation of intracellular survival pathways, with disease progression due to proliferation and resistance to apoptosis, and the emergence of a malignant clone. There are descriptions of MALT lymphomas affecting practically every organ and system, with a marked geographic variability partially attributable to the epidemiology of the underlying risk factors; nevertheless, the digestive system (and predominantly the stomach) is the most frequently involved location, reflecting the gastrointestinal tract’s unique characteristics of contact with foreign antigens, high mucosal permeability, large extension and intrinsic lymphoid system. While early-stage gastric MALT lymphoma can frequently regress after the therapeutic reversal of the chronic immune stimulus through antibiotic eradication of H. pylori infection, the presence of immortalizing genetic abnormalities, of advanced disease or of eradication-refractoriness requires a more aggressive approach which is, presently, not consensual. The fact that MALT lymphomas are rare neoplasms, with a worldwide incidence of 1-1.5 cases per 10^5 population, per year, limits the ease of accrual of representative series of patients for robust clinical trials that could sustain informed evidence-based therapeutic decisions to optimize the quality of patient care.

Key words: Mucosa-associated lymphoid tissue lymphoma; Marginal zone lymphoma; Helicobacter pylori; Gastric lymphoma; Eradication therapy; Nuclear factor-kappa B pathway

Core tip: Mucosa-associated lymphoid tissue (MALT) lymphomas are indolent B-cell lymphomas, originating in acquired MALT induced as a response to a chronic immunoinflammatory stimulus, notably infection by Helicobacter pylori (H. pylori). Antigenic stimulation determines lymphoid hyperplasia; additional genetic aberrations activate survival pathways, with the emergence of a malignant clone. The digestive system (predominantly the stomach) is the most frequent location, reflecting contact with foreign antigens, mucosal permeability and intrinsic lymphoid system. Early-stage gastric MALT lymphoma can regress through the eradication of H. pylori. Immortalizing genetic abnormalities, advanced disease or eradication-refractoriness require treatment alternatives, presently not consensual. Representative clinical trials are needed to optimize patient care.

Pereira MI, Medeiros JA. Role of Helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas. World J Gastroenterol 2014 January 21; 20(3): 684-698. doi:10.3748/wjg.v20.i3.684

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INTRODUCTION

Extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALT) type are indolent, low-grade, mature small B-cell non-Hodgkin lymphoid neoplasms (Table 1) that represent the paradigm for the association between tumorigenesis and a chronic inflammatory stimulus, and are one of the best models of the relationship between specific genetic events and oncogenesis.[3,10]  

Although rare, these neoplasms are clinically relevant due to their unique place in the oncology spectrum as a malignancy that, in many cases, can be cured with a short course of antibiotic therapy.

MALT LYMPHOMAS AND HELICOBACTER

Mucosa-associated lymphoid tissue

Primary lymphoid tissue can be found in the thymus and bone marrow, where lymphocytes differentiate from progenitor cells into functional, mature lymphoid cells. Secondary lymphoid tissue is present in the lymph nodes, in the spleen and in mucosa-associated lymphoid tissue; the latter, with numerous lymphocytes and antigen-presenting cells, develops in the stroma under the epithelium of mucosal barriers that are in contact with the outside environment (gastrointestinal, respiratory and genitourinary tracts), where antigens accumulate and are processed and presented to lymphocytes, as part of a normal adaptive immune response[9]. MALT, like the other components of the immune system, can give rise to a lymphoproliferative disease - the MALT lymphoma. The immune cell of origin of this malignant proliferation appears to be a marginal zone (post germinal center) B-cell present both in lymph nodes and in extranodal tissue, related to plasma cells[7-9].

Despite their association with mucosa-associated lymphoid tissue, MALT lymphomas rarely arise in native physiologic MALT; rather, the majority of cases develop on extranodal acquired MALT infiltrates induced by an immune response to a chronic antigenic stimulus[10,14]. The best studied causal associations are with chronic infections, with the highest levels of evidence being found for gastric MALT and Helicobacter pylori (H. pylori) gastroduodenitis[3,10].

Etiopathogenesis

Chronic antigenic stimulation and the microenvironment: These etiologic associations have led to the hypothesis that chronic or repeated immune stimulation leads to a lymphoid expansion which, in the presence of environmental and microenvironmental factors and a genetic predisposition, can culminate in the emergence of a malignant clone. The mechanisms underlying the antigen-dependence of MALT lymphomas, and the impact of the inflammatory microenvironment, have gradually been elucidated, with tumor progression now known to be driven by an interaction between B-cell receptor (BCR)-derived signals and T-helper (T[+]) cell signals[11].

It has been demonstrated that MALT lymphoma B-cells exhibit polyclonal BCR immunoglobulins, and that direct stimulation by the specific allo- and auto-antigens recognized by these surface antibodies leads to the proliferation of tumor cells; after this oligoclonal expansion, a dominant lymphoma clone can surface through selective pressure[11-13]. BCR polyreactivity has been shown to include simultaneous intermediate affinity to self-antigens (including stomach extract) and foreign antigens (including Helicobacter sonicate), although some authors suggest that polyreactivity is exclusive of tumors carrying t(11;18), and that most other MALT lymphoma antibodies are monoreactive and of high-affinity[13,14].

It has also been shown that MALT lymphomas are infiltrated by type 2 T[+](T[2]) polarized T-cells and that tumor proliferation is enhanced by intratumoral CD4+ T-cells[11]. A large proportion of these CD4+ T-cells are suppressive CD25+ forkhead box P3 (FOXP3) regulatory T-cells (T[reg]), which are themselves recruited by tumor B-cells; higher numbers of tumor-infiltrating FOXP3+ cells confer a better response to H. pylori eradication therapy[11,13].

Bacteria-induced lymphomagenesis: H. pylori infection, generally acquired in childhood, is the most frequent chronic bacterial infection worldwide, and is a major cause of gastroduodenal disease, including chronic gastritis, benign peptic ulcers, gastric carcinoma and gastric MALT lymphoma, although only a very small proportion of H. pylori-infected subjects develop these complications[14,15]. In fact, in a population with an incidence of H. pylori infection of approximately 60%, only 24 cases of gastric MALT lymphoma were observed out of approximately 70000 gastroscopies performed over a period of 18 years[10,21]. The outcome of the infection depends on the host immune response mounted against H. pylori, es-

Table 1 World Health Organization-based classification of mucosa-associated lymphoid tissue lymphomas

| Hierarchical classification | Tumors of hematopoietic and lymphoid tissue | Mature B-cell neoplasms | Non-Hodgkin (B-cell) lymphomas | Marginal zone (B-cell) lymphomas | Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue |
|----------------------------|-------------------------------------------|------------------------|-------------------------------|---------------------------------|---------------------------------------------------------------------|
|                            | Tumors of hematopoietic and lymphoid tissue | Mature B-cell neoplasms | Non-Hodgkin (B-cell) lymphomas | Marginal zone (B-cell) lymphomas | Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue |

Adapted from Swerdlow et al[6], 2008.
Table 2  Recurrent chromosomal translocations described in mucosa-associated lymphoid tissue lymphomas

| Translocation       | Fusion protein          |
|---------------------|-------------------------|
| t(11;18) (q21;q21)  | API2-MALT1              |
| t(1;14) (p22;q32)   | BCL10-IGH               |
| t(1;2) (p22;p12)    | BCL10-IGH               |
| t(14;18) (q32;q21)  | IGH-MALT1              |
| t(5;14) (p14;q32)   | FOXP1-IGH              |

API2: Apoptosis inhibitor 2; MALT1: Mucosa-associated lymphoid tissue translocation protein 1; BCL10: B-cell chronic lymphocytic leukemia/lymphoma protein 10; IGH: Immunoglobulin heavy chain; IGK: Immunoglobulin kappa light chain; FOXP1: Forkhead box protein P1.

pecially the functionality of cytotoxic effector T-cells[10]. This has also been demonstrated for chronic atrophic autoimmune gastritis, secondary to the infiltration and destruction of the gastric mucosa by cytotoxic T-cells specific for H. pylori epitopes that cross-react with the gastric proton-pump[16].

Several arguments support the central role played by H. pylori in MALT lymphomagenesis. Chronic infection with H. pylori is significantly associated with the induction of gastric lymphoid follicles, representing the proposed first step in MALT lymphomagenesis of lymphoid expansion[10]. In addition, H. pylori infection can be demonstrated serologically in most patients, and the bacterium can be histologically identified in the gastric mucosa of the majority of gastric MALT lymphomas, with some series describing incidences as high as 92%, although the density and detectability of H. pylori decrease as the histology progresses from chronic gastritis to gastric MALT lymphoma[10,22-24]. These data suggest that bacterial colonization is important for early lymphomagenesis, but becomes less relevant as the disease progresses; in fact, a monoclonal B-cell clone can be identified in chronic gastritis, before the development of clinical lymphoma[24].

In vivo data in a murine model have shown that infection with Helicobacter spp. is able to reproduce most pathophysiological changes that take place during the early stages of MALT lymphomagenesis[11].

H. pylori eradication through specific antibiotherapy [classical triple therapy with amoxicillin, clarithromycin and a proton-pump inhibitor (PPI), or one of its variations] leads to lymphoma regression in 75% of cases, in a few weeks to 18 mo[30]. The odds of success associate with the clinical stage, being very high for early-stage lymphomas, lower for more advanced stages and practically nil once the serosa is breached. These observations also support the hypothesis that H. pylori-independence is a feature of lymphoma progression, associated with the acquisition of additional genetic alterations[30]. This aspect parallels the finding in gastric carcinoma (the intestinal type primarily associated with H. pylori infection) that the absence of active infection by H. pylori is a significant adverse prognostic factor, with one series finding a decrease in 10-year overall survival (OS) in locally advanced disease, from approximately 70% in H. pylori-positive patients to just over 20% in H. pylori-negativity[25].

The relationship between chronic infection with H. pylori, microenvironment and lymphomagenesis has been strengthened by the fact that tumor cells only proliferate in response to strain-specific H. pylori cell preparations when in the presence of tumor-infiltrating T-cells; on the other hand, the latter expand in response to H. pylori stimulation even when isolated from the tumor micro-environment[30]. The elimination of the stimulus to the T-cell expansion that sustains tumor-growth, through the eradication of H. pylori, leads to tumor regression[31]. The central role that tumor microenvironment T-cells play in MALT lymphomagenesis means that the modulation of local T-cell immunity could be an attractive therapeutic approach[31].

It has been suggested that lymphomagenesis and genetic aberrations are also facilitated by DNA-damage caused by reactive oxygen species produced by neutrophils as part of the immune response to an infection by H. pylori strains positive for the virulence factor cytotoxin-associated gene A (CagA)[32]. In fact, CagA-positive strains associate with higher grades of mucosal inflammation, severe atrophic gastritis and gastric carcinogenesis, and activate the phosphoinositide 3-kinase/AKT pathway, an anti-apoptotic, pro-proliferative survival pathway, contrary to CagA-negative strains[28,29].

Genetics of MALT lymphoma

Lymphomas present with several genetic aberrations, including translocations, point mutations, gene amplifications and deletions of genes (including tumor suppressors), some of which have been shown to have diagnostic and prognostic value. Non-random chromosomal translocations involving a limited group of genes are characteristic[33]. In MALT lymphomas, 5 recurrent cytogenetic alterations have been described, converging on the same intracellular pathways[31] (Table 2).

Genes and signaling pathways: The immunoglobulin (Ig) heavy chain gene (IGH) is frequently involved in translocations in MALT lymphomas and other lymphoproliferative diseases, as a consequence of the chronic antigenic stimulation which underlies the Etiopathogenesis of these neoplasms and the central role played by the BCR in lymphomagenesis[10]. The Ig kappa light chain (IGK) and lambda light chain genes can likewise be involved, through the same mechanism. In fact, B-lymphoid cells, as part of their normal immune response, undergo rearrangements of the Ig genes as part of somatic hypermutation and class-switch recombination[34]. These directed mutations originate a localized genetic instability that can lead to aberrant rearrangements, with the juxtaposition of oncogenes to Ig gene enhancers[32]. The continued enhancer activation as a normal response to immune stimulation will, in turn, result in the overexpression of the activated oncogene, with inflammation driving oncogenesis.

Normal lymphocyte function depends on the strict
Antigen stimulation of the BCR recruits B-cell chronic lymphocytic leukemia/lymphoma protein 10 (BCL10) to the antigen-receptor complex and this protein, in turn, links BCR signaling to the NF-κB pathway, through its interaction with mucosa-associated lymphoid tissue translocation protein 1 (MALT1). MALT1 oligomerizes with BCL10, leading to the downstream activation of NF-κB. In the absence of oligomerization, wild-type MALT1 is incapable of activating NF-κB; however, when it oligomerizes in the absence of BCL10, it acquires the NF-κB-activating ability of the hetero-oligomer - MALT1 activity and NF-κB activation are thus dissociated from upstream signaling originating in the surface BCR and, consequently, from antigen stimulation. BCL10 also acquires the ability to constitutively activate NF-κB independently of antigenic stimulation, when it is overexpressed, such as when it is brought under the control of hyperactive promoter or enhancer regions, through chromosomal translocations. None of these alterations, however, are independently sufficient for MALT lymphomagenesis, and the interaction with other immune, genetic and environmental factors is probably necessary for continued tumor growth.

Recurrent translocations: Rearrangements of the genes encoding the proteins described above - MALT1, BCL10, IGH and IGK - as well as API2 and forkhead box P1 gene (FOXP1), result from the 5 recurrent translocations that have been described for MALT lymphoma (Table 2). The three most common and characteristic translocations - t(11;18) (q21;q21), t(1;14) (p22;q32) and t(14;18) (q32;q21) - are present with variable frequency depending on the tissue of origin of the lymphoma. They generate oncogenic fusion proteins that activate the NF-κB pathway, and lymphomas with these translocations show an overexpression of NF-κB target genes.

The t(11;18) (q21;q21) results in the chimeric fusion of apoptosis inhibitor 2 (API2) and MALT1, originating a transcript that codes a functional fusion protein that has the ability of MALT1 to activate NF-κB but is controlled by the API2 promoter, which is itself stimulated by NF-κB. Therefore, this fusion gene results in a positive feedback cycle that leads to the unregulated, constitutive activation of NF-κB. The API2-MALT1 fusion oncoprotein also contributes to the constitutive activation of NF-κB through an additional alternative non-canonical pathway. Thus, this translocation is an important driver of MALT lymphomagenesis, immortalizing the cell and releasing it from BCR-antigen-dependence for its NF-κB activation and survival. This is in agreement with the clinical observations that the presence of t(11;18) correlates with resistance to a successful eradication of H. pylori, that patients who respond to eradication therapy are generally negative for the fusion transcript, and that its presence is more frequent in H. pylori-negative than H. pylori-positive patients, suggesting that the latter need chronic stimulation of their BCR by antigen-antibody complexes for lymphoma cell survival. The NF-κB-activating translocations t(1;14) and t(14;18) have similarly been noted to be associated with bacterial eradication-resistance.

Notably, t(11;18) is the most common structural chromosomal abnormality described in MALT lymphomas, being particularly frequent in gastric (reports ranging from 10%-35%), colon, and pulmonary lymphomas. It has a very high specificity (being exclusive or nearly-exclusive) for the MALT subtype, is the most specific of the recurrent translocations in these neoplasms, and is of high diagnostic value. It is absent from non-complicated H. pylori-positive gastritis but often found in gastric MALT lymphoma patients infected with CagA-positive H. pylori. The transcript is rarely present in MALT lymphomas with areas of high-grade (diffuse large B-cell lymphoma, DLBCL) transformation, leading some authors to consider it exclusive of low-grade cases. On the other hand, it associates with advanced stages and submucosal involvement, being absent from lymphomas restricted to the mucosa.

The t(14;18) (q32;q21) results in the fusion of IGH with MALT1, inducing the overexpression of MALT1, which oligomerizes and activates NF-κB. This translocation is virtually absent from gastric locations, but variably common in different extragastric tumors, with reports ranging from 20% of salivary gland to 100% of hepatic tumors. The t(1;14) (p22;q32) induces the juxtaposition of BCL10 with the IGK gene enhancer region, with a resulting overexpression of BCL10 and activation of NF-κB. In the t(1;2) (p22;p12) variant, BCL10 is juxtaposed to IGK, originating an identical overexpression of BCL10. The two variants, though characteristic of MALT lymphomas, are found in under 4% of described cases and associate frequently with other cytogenetic aberrations, such as trisomy 3.

The t(3;14) (p14;q32) apposes the FOXP1 with the IGH enhancer, resulting in the overexpression of the former. FOX family proteins have been shown to be involved in signal transduction that mediates proliferation, differentiation and the immune response. Though its precise mechanism of action remains to be clarified, in MALT lymphoma (as in DLBCL) FOXP1 overexpression...
has been described as an adverse prognostic factor\(^{[46-51]}\). Like t(14;18), its frequency varies among different anatomical locations, with the original series describing incidences ranging from 0% in gastric locations to 50% of thyroid samples\(^{[40]}\).

**Other somatic alterations:** Apart from the characteristic translocations, several other somatic genetic alterations can be identified in MALT lymphomas, including numeric chromosome aberrations and allelic imbalances. The specific frequencies of each genetic aberration vary in the literature, with reports addressing distinct lymphoma locations and stages, using differing methodologies and focusing on series from separate geographical locales. It has been suggested that these geographical differences reflect a true heterogeneity in the distribution of genetic aberrations, and not just different sampling methods, and that the different anatomical locations are a reflection of distinct processes of lymphomagenesis\(^{[44,52]}\).

**Epidemiology**

MALT lymphomas represent approximately 7% of newly-diagnosed lymphomas\(^{[8]}\). They are a rare malignancy, with a worldwide incidence estimated at 1-1.5 cases per 10\(^5\), per year\(^{[5]}\). Gastric cancer, in comparison, is 5 to 10-fold more frequent (United States National Cancer Institute Surveillance Epidemiology and End Results data). As with other indolent lymphomas, the incidence increases with age, with the majority of patients being over 50 years old (with a median of 61)\(^{[5]}\).

These lymphomas can affect practically all organs and systems, although different anatomical locations have a large geographic variability, which has been partially attributed to a distinct epidemiological risk factor distribution\(^{[53]}\). Overall, the digestive system is the most frequently involved location, reflecting the gastrointestinal tract’s unique characteristics of contact with foreign antigens, mucosal permeability, large extension and intrinsic lymphoid system\(^{[10,45,54]}\). In fact, MALT lymphomas represent a large proportion of all gastrointestinal lymphomas: in a revision of B-cell gastrointestinal lymphomas, one-fifth were pure MALT lymphomas and a further 8% were MALT lymphomas with a DLBCL component\(^{[53]}\). Gastrointestinal involvement by B-cell lymphomas is most common in the stomach (which accounts for 60%-75% of gastrointestinal lymphomas, and for over 50% of all MALT locations), followed by the small intestine, colon and rectum\(^{[10,18,45,65]}\).

The involvement of various non-contiguous sites (including both different systems and discrete segments of the same system, such as different aspects of the gastrointestinal tract, separated by healthy tissue) is common in MALT lymphomas, both at diagnosis and throughout the evolution of the disease, and has been interpreted as recurrence, dissemination or independent synchronous or metachronous development\(^{[12,19,64]}\). There are descriptions of the concomitance of MALT lymphoma with other lymphomas and even with other malignancies, such as the coexistence of primary gastric MALT lymphoma and Epstein Barr virus-associated gastric carcinoma, or of colonic adenocarcinoma and gastric MALT\(^{[61-63]}\). It has been proposed that, in these circumstances, treatment decisions should prioritize the tumor with the worst prognosis at the moment of diagnosis, which is generally the carcinoma\(^{[64]}\).

**Diagnosis**

The diagnosis of MALT lymphoma rests on the clinical suspicion of a lymphoproliferative disease or another malignancy, confirmed by histopathologic data; the latter must be complemented by the judicious use of immunohistochemistry (and eventually flow cytometry), cytogénetics and molecular biology, moreover considering that the histological differential diagnosis between severe gastritis and early stage lymphoma can be difficult\(^{[46]}\).

**Histopathology:** The histopathologic evaluation of a tissue biopsy sample remains fundamental for the diagnosis of MALT lymphoma. This lymphoma is characterized by the presence of a typical infiltrate located in the marginal zone of follicles with reactive germinal centers, with possible extension into the interfollicular region, made up of small, morphologically heterogeneous mononuclear B-cells, originating in post-germinative memory cells, and including centrocyte- like marginal zone cells, monocytoid B-cells, immunoblastic and centroblast-like cells; plasmocytes can be seen in the sub-epithelial zones and are monoclonal in up to half of cases\(^{[4,10,18,54,45]}\). Pathologic acquired MALT and MALT lymphomas are similar to physiological MALT\(^{[4]}\). Therefore, the principal diagnostic criterion for MALT lymphoma is the invasion and destruction of the adjacent epithelium, originating typical lymphoepithelial lesions, as described by Wotherspoon, although the European Society for Medical Oncology (ESMO) has recently determined by consensus that the presence of these lesions is neither essential for, nor specific of, a diagnosis\(^{[10,12,22,63]}\). Immunohistochemistry can be a valuable aid in the differentiation between MALT lymphomas and other small cell lymphomas, including follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and even mantle-cell lymphoma (MCL)\(^{[18,43]}\) (Table 3). Immunophenotyping can also contribute to the differential diagnosis between small cell lymphomas\(^{[46]}\). MALT lymphoma B-cells have an immunophenotype that is identical to the normal phenotype of a non-neoplastic marginal zone lymphocyte, with positivity for the B-cell surface markers CD19, CD20 and CD22 and negativity for CD5 (unlike CLL/SLL), cyclin D1 (unlike MCL) and CD10\(^{[18,6,10,45]}\). Malignant cells exhibit light-chain restriction, as a marker of clonality\(^{[22]}\). It has been further suggested that the microRNA signature can be informative in the distinction between gastritis and MALT lymphoma\(^{[67]}\).

Although MALT lymphoma is a low-grade disease, with large transformed cells being rare in the neoplastic infiltrate, it can undergo transformation to an aggressive
Abnormal scans

High-grade lesions

Table 3  Useful phenotypic markers for the differential diagnosis of mucosa-associated lymphoid tissue lymphoma

| Antigen      | Notes                                    |
|--------------|------------------------------------------|
| sIg̣         | B-cell receptor                          |
| CD19⁺        | Pan-B-cell marker                        |
| CD20⁺        | Pan-B-cell marker                        |
| CD22⁺        | Pan-B-cell marker                        |
| CD79a⁺       | Pan-B-cell marker                        |
| CD5          | Positive in CLL/SLL                      |
| CD10         | Positive in follicular lymphoma          |
| CD22         | Positive in CLL/SLL                      |
| Cyclin D1    | Positive in mantle cell lymphoma         |

CD: Cluster of differentiation; sIg: Surface immunoglobulin; CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma.

diffuse large B-cell lymphoma (the most common histological type of primary gastric lymphoma, representing over half of cases), through poorly understood mechanisms [43,31,68]. Transformed MALT/DLBCL appears to have a similar prognosis to de novo DLBCL, with overlapping progression-free and overall survival [69].

Cytogenetics and molecular biology: The identification of the characteristic recurrent chromosomal translocations, by conventional cytogenetics, FISH or molecular biology, is informative and can contribute to the differential diagnosis of MALT lymphoma, as described above.

Medical image: Imaging studies are fundamental not only for the diagnosis but also for the adequate staging of the lymphoma at presentation.

Esophagogastroduodenoscopy with multiple biopsies is the gold standard for the diagnosis of gastric MALT lymphoma. In a 24-patient series, the most common endoscopic findings were mild hyperemia (67%), superficial erosions (17%) and superficial ulcers (17%) [30]. Gastric ulcers, especially when unresponsive to conventional treatment, should be biopsied due to the risk of malignancy; although gastric carcinoma is the usual finding in malignant gastric ulcers, some cases of gastric lymphoma can also present as ulcers, including with local complications, such as perforation [30]. Push enteroscopy with serial biopsies is safe and easy, and can detect the synchronous involvement of the duodenum and jejunum by MALT lymphoma, a finding that was present in 11% of patients in a retrospective series [59]. Colonoscopy is also able to identify macroscopic changes in the mucosa (such as discoloration with a reduction of superficial vessels) in colorectal MALT lymphoma and, according to some authors, should also be part of the diagnostic workup of gastric MALT lymphoma to screen for metachronous involvement [71]. Serial esophagogastroduodenoscopies with multiple biopsies are mandatory for the follow-up of post-remission gastric MALT lymphoma, especially in early-stage disease, where recurrence tends to be localized to the mucosa and undetectable by other imaging modalities [31].

It has been suggested that the use of magnified en-

doscopy techniques for the evaluation of the microstruc-
tural pattern of the lesion and distribution of abnormal vessels could be useful both for diagnosis and follow-up [73]. In a series of patients with localized gastric disease, nonstructural areas with abnormal vessels were present at magnified esophagogastroduodenoscopy in all patients at diagnosis, disappearing with histopathologic remission [73]. Compared to histopathology, nonstructural areas had a sensitivity of 77% and a specificity of 87%, while the presence of abnormal vessels had both a sensitivity and specificity of 86% [73].

Endo Ultrasonography enables the endoscopist to evaluate the degree of organ involvement and infiltration of contiguous structures in a single procedure, which is fundamental for staging [69]. The presence of diffuse parietal thickening in endo-ultrasonography is suggestive of infiltration by lymphoma [71]. The ultrasonographic appearance of MALT lymphoma can be characteristic in some locations, and it has been suggested that when sonographic findings are characteristic, excisional biopsy can be replaced by ultrasound-guided core-needle biopsy [74].

Abdominal computerized tomography (CT) can detect locally advanced gastric MALT lymphoma, presenting as a diffuse or localized parietal thickening, as well as lymphadenopathy, local complications (including perforation) and hepatosplenomegaly [75]. Gastrointestinal dissemination can manifest as circumferential parietal thickening of an intestinal segment, or localized polyoid masses with homogeneous and isoattenuating or hypointensating enhancement [71,76]. Three-dimensional reconstruction in gastrointestinal lymphomas correlates with the underlying histopathology, with an increased likelihood of low-grade gastric MALT lymphoma in patients with normal scans, with minimal gastric wall thickening (5-10 mm) or with small depressed lesions with vague margins [76] (Table 4). On the other hand, a severe diffuse thickening of the gastric wall (> 10 mm), focal well-demarcated masses, or masses with homogeneous attenuation and mild contrast enhancement, suggest high-grade lesions; perigastric adenopathies are also more likely in the latter than in low-grade lymphoma [76]. In contrast, multiple lymphomatous polyposis is common in MCL, a bulky mass with uniform isoattenuating in the right lower quadrant suggests Burkitt lymphoma, and thickened nodular folds with multiple ulcerative lesions, perforations and obstruction are typi-
Table 5 Comparison of four frequently used staging systems for primary gastrointestinal lymphomas

| Tissue invasion | Ann Arbor | Radakiewicz | Lugano | Paris |
|-----------------|-----------|--------------|--------|-------|
| Gastrointestinal tract | I E | I E | I | T1 N0 M0 |
| Mucosa or submucosa | I E | I E1 | I | T1 N0 M0 |
| Mucosa | I E | I E1 | I | T1m N0 M0 |
| Submucosa | I E | I E1 | I | T1sm N0 M0 |
| Muscularis propria or subserosa | I E | I E2 | I | T2 N0 M0 |
| Serosa | I E | I E2 | I | T3 N0 M0 |
| Intra-abdominal extension | I E | I E | II E | T4 N0 M0 |
| Adjacent tissues or organs | II E | II E | II | T1 N1 M0 |
| Regional lymph nodes | II E | II E | II | T1 N1 M0 |
| Infradiaphragmatic distal lymph nodes | II E | II E | II | T1 N2 M0 |
| Disseminated disease | IV | IV | IV | T3 N3 M0 |
| Supradiaphragmatic lymph nodes | IV E | IV E | IV | T4 N2 M0 |
| Non-contiguous gastrointestinal | IV E | IV E | IV | T1 N1 M1 |
| Non-contiguous metastasisa | IV E | IV E | IV | T1 N1 M2 |
| Marrow involvement | IV E | IV E | IV E | T1 N1 M2 B1 |

In the case of synchronous lesions originating in the gastrointestinal tract, staging refers to the characteristics of the most advanced lesion. Note that the Lugano system does not include a stage II. Any subtype of tumor extension (T1 to T4) or nodal (N0 to N3) or metastatic (M0 to M2) involvement; Non-contiguous gastrointestinal involvement refers to the presence of lymphoma in more than one gastrointestinal site with segments of discontinuity that are free of disease (such as the involvement of the stomach and rectum, with a free small intestine and bowel); Including the non-contiguous involvement of the peritoneum. References for the 4 staging systems are given in the main text.

Table 6 Tumor-node-metastasis staging system qualifiers

| Stage | Definition |
|-------|------------|
| Tumor | Tx Extension of lymphoma not established |
| Nodes | Nx Nodal involvement not evaluated |
| Metastasis | Mx Dissemination of lymphoma not evaluated |
| Bone marrow | Bx Bone marrow infiltration not evaluated |

Table 7 International prognostic index for aggressive B-cell lymphomas

| Prognostic factor | Quantification |
|-------------------|----------------|
| Advanced age | > 60 yr |
| Advanced stage | Ann arbor stages III or IV |
| High tumor burden and activity | Increased serum lactate dehydrogenase |
| Poor performance status | ECOG > 2 |
| Multifocal distribution | Two or more extranodal sites |

The International Prognostic Index is calculated by adding 1 point for each adverse risk factor. ECOG: Eastern Cooperative Oncology Group performance status scale.

Study Group proposed the Paris System [tumor-node-metastasis (TNM)-B], an adaptation of the existing TNM system in mainstream use for the classification of non-hematologic solid malignancies, for the staging of primary gastrointestinal lymphomas[81] (Tables 5 and 6).

Prognosis

Most MALT lymphomas are at diagnosis characterized by non-disseminated (early-stage) disease, with both marrow and distal nodal involvement being rare, although regional lymph node infiltration is relatively frequent in gastric MALT lymphomas[83]. Staging alone is not sufficiently predictive of disease outcome in lymphoproliferative diseases, with survival being influenced by several concurrent prognostic factors. To adequately integrate all these factors into the clinical decision, prognosis can be quantified in B-cell lymphomas through internationally validated scales or indices, such as the International Prognostic Index (IPI), which was developed for aggressive B-cell lymphomas[84] (Table 7). There is no prognostic index that is specific for MALT lymphomas. However, it has been demonstrated that IPI scores correlate significantly with time to relapse in MALT lymphomas, differentiating low, low-intermediate and high risk groups; on the other hand, data regarding the utility of the FLIPI (follicular lymphoma IPI) in this group of patients is contradictory[83,84]. Additional indicators of poor prognosis include the presence of a large-cell component at diagnosis, B symptoms (unexplained fever, night sweats and unintentional weight loss), high serum β2-microglobulin or serum lactate dehydrogenase, low serum albumin, bone marrow failure (evidenced by anemia or thrombocytopenia), advanced

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age (over 60 years) or poor performance status (2 or above on the WHO/Eastern Cooperative Oncology Group scale), and the presence of a bulky tumor. The presence of extragastric disease also appears to have prognostic value. The absence of complete remission with first-line treatment is a further a posteriori indicator of poor prognosis. We have discussed above how genetic aberrations, such as the presence of the t(11;18), correlate with resistance to treatment. Rearrangements of the BCL6 locus, or BCL6 protein overexpression, appear to associate with large-cell transformation of MALT; OS in de novo and MALT-transformed gastric DLBCL correlates strongly with BCL6 overexpression.

Treatment
Current guidelines are consensual in indicating *H. pylori* eradication as the first line approach in gastric MALT lymphoma. However, due to the paucity of extensive series of patients with MALT lymphomas and, more importantly, of prospective clinical studies, the optimal treatment of *H. pylori*-negative and eradication-resistant *H. pylori*-positive gastric lymphomas has not been convincingly established. Therefore, different centers report a variety of approaches, many of which have relevant side-effects.

These lymphomas follow an indolent clinical course with prolonged OS (80% at 5 years) and disease-free survival, on par with other low-grade lymphomas and, in early stage disease, tend to respond to a wide variety of treatment approaches; however they are characterized by a high recurrence rate, with most patients relapsing within 5 years, often in organs with acquired MALT that are distant from the original location. Second remissions can be regained with retreatment; however, the disease-free interval tends to decrease after each subsequent remission. Early-stage disease tends to remain localized for a long time, and responds satisfactorily to local treatment approaches, such as surgery or radiotherapy. However, survival correlates inversely with the stage at diagnosis (90%-95% at 5 years for stage I, 75% for stage II and as low as 30% for stage IV), with about one-third of patients presenting with advanced disseminated disease at diagnosis and requiring systemic treatment.

Antibiotherapy: Since MALT lymphomas are indolent neoplasms, in selected patients with asymptomatic or minimally-symptomatic non-gastric MALT lymphoma without a large-cell component, a strategy of expectant active surveillance of the patient (watchful waiting) with repeated imaging studies and hematological monitoring can be the most adequate approach at diagnosis, moreover due to the possibility of spontaneous regression of MALT lymphomas, which can occur even when there is unequivocal histological confirmation of the lesion and when there is a transformed high-grade component.

On the other hand, the antibiotic eradication of *H. pylori* infection is the first line treatment for gastric MALT lymphomas in Ann Arbor Stage I E (representing the majority of tumors at diagnosis), leading to a complete endoscopic and histopathologic remission with an excellent prognosis and the possibility of cure in approximately 80% of patients (most patients in Stage I E1 and a smaller proportion of patients in stage I E2), while lymphomas in Stage II E and above are usually less responsive; regression of Stage I E (and some II E) gastric DLBCL, both de novo and transformed from MALT, following *H. pylori* eradication therapy, has also been described. Although the probability of MALT lymphoma regression in response to a successful *H. pylori* eradication is influenced by the patient's cytogenetics, through the mechanisms described above, it has been suggested that introducing empiric eradication therapy in the absence of molecular testing is clinically justified, due to the high remission rates that can be achieved. Nevertheless, when these methods are available, testing for t(11;18) could be a helpful a priori predictor of response to therapy.

Testing for *H. pylori* infection should be performed in all patients with gastric MALT lymphoma, through esophagogastroduodenoscopy with biopsy (for histopathology, culture or a rapid urease test); through a fecal antigen test; or through a urea breath test. Comparing the available tests for *H. pylori*, the antigen test has been noted to have a higher sensitivity and negative predictive value (both 100%) than the rapid urease test, while the latter was found to have a higher specificity and positive predictive value. PPI should be suspended at least one week before testing. Irrespective of the test results, the ESMO consensus is that eradication therapy must be given to all gastric MALT lymphomas, independently of stage or histological grade.

The first line therapy for eradication is the triple approach between a PPI, clarithromycin and either metronidazole or amoxicillin. In special select cases, the antibiotics may have to be selected through an antibiotic sensitivity test, as in the case of known antibiotic allergies. Successful eradication should be confirmed by repeat testing for *H. pylori* four weeks or more after completion of therapy, due to potential treatment failures, which are partly due to compliance issues. We have described a failed eradication rate of nearly 20% with an amoxicillin/clarithromycin/PPI association, in a population of unselected *H. pylori*-positive patients without gastric lymphoma, despite *ex vivo* sensitivity of all strains to the two antibiotics used. In the case of treatment failure, eradication should be re-attempted with a quadruple association of a PPI, tetracycline, metronidazole and a bismuth salt.

While over 80% of patients can achieve a complete lymphoma remission (according to GELA criteria; with successful *H. pylori* eradication, there are no clear predictive factors for lymphoma response to eradication, and primary refractoriness can be found in 10%-20% of low-grade gastric MALT lymphomas). In a series of Ann Arbor Stage I E1 patients, there were 7% of non-responders, who were not different from responders in gender, age, endoscopic appearance or large-cell
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**Table 8 Chemotherapy treatment options in American and European guidelines**

| Drug group          | Drugs                                      |
|---------------------|--------------------------------------------|
| Alkylators          | Chlorambucil<sup>1</sup>                   |
|                     | Cyclophosphamide<sup>1,2</sup>            |
|                     | Bendamustine<sup>1,2</sup>                |
| Purine nucleoside analogues | Fludarabine<sup>1,2</sup> |
|                     | Cladribine<sup>2</sup>                    |
| Anthracyclines and anthrancediones | Doxorubicin<sup>1</sup>                 |
|                     | Mitoxantrone<sup>2</sup>                  |
| Vinca alkaloids     | Vincristine<sup>2</sup>                   |

Reflecting the lack of clear consensus, current guidelines propose different associations of these agents as monotherapy, combination chemotherapy, and combined immunochemotherapy with rituximab. European Society for Medical Oncology 2013 guidelines; *National Comprehensive Cancer Network 2011 guidelines.*

The fact that gastric MALT lymphoma regression, in response to *H. pylori* eradication, can take up to 18 mo, means that refractoriness should not be assumed prematurely, and determines a compulsory extended follow-up period, with regular esophagogastroduodenoscopies and repeat biopsies to demonstrate complete remission, although the optimal frequency of endoscopic evaluation has not been definitely established<sup>[4,10]</sup>. A period of watchful waiting with repeated esophagogastroduodenoscopic biopsies has also been proposed as a valid option after successful gastric MALT lymphoma regression following eradication<sup>[107]</sup>. The fact that 5% of patients with gastric MALT lymphoma in complete remission develop local metachronous gastric carcinoma despite *H. pylori* eradication (an incidence reported to be 6 to 9-fold that of the general population), diagnosed by long-term endoscopic follow-up, also underlines the importance of close endoscopic surveillance<sup>[106,108]</sup>. Nevertheless, the ideal duration of the follow-up period after initial eradication treatment remains to be defined, with some authorities suggesting immediate treatment after a successful eradication without lymphoma remission, while others propose continued watchful waiting<sup>[107]</sup>. The identification of resistance-associated genetic aberrations, such as t(11;18), could be an indication of true refractoriness to eradication, guiding therapeutic decisions. Likewise, the presence of a large-cell component should help inform a choice to opt for alternative therapies if eradication fails to induce regression. The presence of symptoms that interfere with the patient’s quality of life is an indication to suspend watchful waiting and introduce treatment<sup>[109]</sup>.

Complete remissions that are achieved through *H. pylori* eradication are prolonged. In a series of stage I E1 patients in complete remission, after a median of 35 mo of follow-up only 5% showed lymphoma recurrence, which was limited to the mucosa and only detectable on endoscopic biopsies<sup>[23]</sup>. In 57% of these patients, recurrence was associated with re-infection with *H. pylori*, and regressed after re-eradication; the tumors in the remaining patients were *H. pylori*-negative and regressed spontaneously<sup>[23]</sup>. The presence of persistent minimal histological residuals after *H. pylori* eradication with endoscopic normalization can be managed through a watchful waiting approach with regular endoscopic biopsies, with over 95% of patients either maintaining stable minimal histological residuals or eventually achieving a complete response, as was demonstrated by two series of over 100 patients<sup>[98,107,108]</sup>.

Although there have also been descriptions in small series of regression of *H. pylori*-negative MALT lymphomas after eradication therapy, which have been interpreted by the authors as being causally related, the physiopathologic basis for this finding needs to be further explained<sup>[105,111]</sup>.

**Local treatment approaches:** In gastric MALT lymphoma, the current view is towards stomach-conserving conservative treatment, avoiding first-line surgical resection<sup>[98]</sup>. Nevertheless, a surgical approach can be curative in MALT lymphomas, especially when the lymphoma is an unexpected finding after resection, or collocates with a more aggressive carcinoma that is completely resected<sup>[61,112,113]</sup>. Regardless of curative intent, an invasive approach can be indicated in the first line for the control of local complications of the tumor.

Radiotherapy has a high curative potential in the stomach-conserving treatment of gastric MALT lymphoma, in *H. pylori*-negative patients or following a lack of response to eradication in *H. pylori*-positive cases, with 80% of eradication-refractory patients achieving a complete remission with radiotherapy; a dose of 30-40 Gy in 15-20 fractions has been proposed<sup>[58,98,106,114]</sup>.

**Chemotherapy:** Eradication-refractory gastric MALT lymphomas have high rates of response to chemotherapy, and this is a valid approach after confirmed failure of first-line eradication. Likewise, it is justified in systemic disease with *a priori* dissemination. In contrast, the use of chemotherapy in localized MALT lymphomas after a successful response to *H. pylori* eradication, proposed by some authors to prevent recurrence, is still controversial, with no evidence to support it<sup>[65,115]</sup>.

Several chemotherapeutic drugs have been assayed when systemic therapy is warranted, both as single-agent treatments and in combinations, in case-series reports or in small-sized clinical trials, with varying results, depending on the anatomical location and the stage of the lymphoma (Table 8). Advances have been scarce in the 6 years since the extensive treatment review by Morgner and colleagues; as of 2013, there is no definitive data to support the choice of one modality of systemic treatment over the others, and the benefit of chemotherapy over local treatment approaches in earlier stage disease is still not clear<sup>[60,106]</sup>. A controlled prospective clinical trial of early-stage (I E and II E) gastric MALT lymphoma comparing surgery, radiotherapy, and chemotherapy with
cyclophosphamide, vincristine and prednisolone, with or without doxorubicin (CVP/CHOP), showed a significantly higher event-free survival with combination chemotherapy, compared to either surgery or radiotherapy, but with identical OS in all three arms. It has been noted that tumor microenvironment T-cells play an important role in lymphomagenesis induced by chronic antigenic stimulation, underlying the potential utility of chemotherapeutic agents that simultaneously target malignant B-cells and microenvironment T-cells, such as single-agent nucleoside analogues. Fludarabine demonstrated a significant reduction in peripheral blood T-cells, compared to eradication alone, while in biopsy samples there was an increase in Treg. Cladribine achieved a complete response rate of 100% in primary gastric lymphomas, with an overall (gastric and extragastric) survival at 80 mo of 84%. On the other hand, the T-cell modulation associated with nucleoside analogues such as fludarabine and cladribine can lead to long-term immunosuppression and increased infectious risk, with increased morbidity. A phase II trial of gemcitabine, a less T-suppressive analogue expected to overcome this problem, was discontinued due to disappointing results.

Single-agent alkylators, including chlorambucil and bendamustine, have shown clinical effectiveness with acceptable toxicity, demonstrating that this is another valid treatment approach. However, it has been suggested that t(11;18) is a marker of non-response to alkylating regimens. Several of the newer agents have also been tried in gastric MALT lymphomas. Thalidomide is an antiangiogenic and immunomodulatory drug with anti-NF-kB activity, which justifies its potential utility in MALT lymphomas. It has been used as a salvage therapy in a series of H. pylori eradication-refractory chemo-resistant gastric MALT lymphomas, with an overall response rate (ORR) of 0% in patients with the API2-MALT1 transcript and of 86% in patients without the transcript; the latter (but not the former) showed a significant downregulation of the expression of NF-kB in residual neoplastic cells and tumor microenvironment. These data suggest that the presence of t(11;18) is also predictive of non-response to thalidomide.

The role of the ubiquitin proteasome system (UPS) in the regulation of the NF-kB pathway serves as the rationale behind the use of proteasome inhibitors in the treatment of MALT lymphomas. Previous basic and clinical experience with these agents has demonstrated that they disrupt multiple UPS-dependent cellular pathways, with apoptosis as the final event. However, trials of bortezomib have demonstrated high rates of toxicity at full-dose, which persisted with a reduced-dose protocol that had an ORR under 50%. Given the indolence and prolonged survival of MALT lymphoma, acute and long-term toxicity should be taken into account when interpreting results and comparing risk-benefit ratios of different treatment approaches.

Monotherapy with an anti-CD20 monoclonal antibody (rituximab) can induce sustained complete remissions of MALT lymphoma, with descriptions of success in both localized and systemic disease, and with retreatment at relapse leading to reinduction of complete remission. In MALT lymphoma, as in other B-cell lymphomas, rituximab has also been used as part of combination immuno-chemotherapy and radiotherapy, with good results, improving the responses to single-agent or multiple-agent chemotherapy, with tolerable side-effects. However, some trials suggest that time to progression was not improved, while others fail to find an improvement with rituximab, results that highlight the importance of starting well-designed phase III studies that can clarify the role of the various treatment approaches and of combination modalities.

An alternative to rituximab is radio-immunotherapy with Y-ibritumomab tiuxetan, an anti-CD20 monoclonal antibody containing a radioactive isotope that was able to induce high rates of complete remissions of up to 24 mo in highly treated refractory patients, while permitting a ten-fold reduction in the dose radiotherapy, potentially overcoming some of the local complications of the latter.

CONCLUSION

MALT lymphomas are rare and heterogeneous malignancies that occupy a unique position in the spectrum of oncologic disease, as they can potentially be cured with a simple course of antibiotics. Nevertheless, as indolent lymphomas, they present to the clinician the singular challenge of having to identify the optimum balance between effective therapy and minimal toxicity for a neoplastic disease that can have a decades-long course of remission and relapse, often in the absence of robust data and representative series on which to sustain an evidence-based practice of medicine.

The known association of gastric MALT lymphoma with chronic immune stimulation through H. pylori infection has offered invaluable insights into lymphomagenesis and, by extension, the mechanisms of neoplastic transformation in general. The knowledge thus acquired has, in turn, exposed key molecules of cell-cycle regulation, survival, apoptosis and proliferation, which can be manipulated as specific therapy targets. Such findings can often be reciprocally translated between MALT lymphomas and other lymphoproliferative and plasma cell diseases, which share common pathways of malignization.

The clinical translation of these findings must, necessarily, rely on strengthened long-term multicentric international collaborations to enable the accrual of representative numbers of patients for epidemiologic studies and prospective, randomized, blinded clinical trials. Only then can we hope to move towards the truly targeted, personalized treatment approach that these patients require.
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