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TOPIC HIGHLIGHT

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Role of *Helicobacter pylori* in gastric mucosa-associated lymphoid tissue lymphomas

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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.

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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[1-5].

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[6]. 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[3,10]. 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_h) cell signals[11].

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

Hierarchical classification of mucosa-associated lymphoid tissue lymphomas, according to the 2008 World Health Organization definitions. Adapted from Swerdlow *et al*[5], 2008.

It has been demonstrated that MALT lymphoma B-cells exhibit polyreactive surface BCR immunoglobulins, and that direct stimulation by the specific allo-antigens 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_h (T_h2)-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_{regs}), which are themselves recruited by tumor B-cells; higher numbers of tumor-infiltrating $FOXP3^+$ cells confer a better response to *H. pylori* eradiation therapy[11,15].

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[16-19]. 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[20,21]. The outcome of the infection depends on the host immune response mounted against *H. pylori*, es-

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-IGK
t(14;18) (q32;q21)	IGH-MALT1
t(3;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[16]. 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[20]. 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 [classic 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[10]. 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[10]. This aspect parallels the finding in gastric carcinoma (the intestinal type primarily associating 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 microenvironment[26]. The elimination of the stimulus to the T-cell expansion that sustains tumor-growth, through the eradication of *H. pylori*, leads to tumor regression[26]. 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[27].

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)[10]. 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[30]. 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[32]. 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

regulation of the transcriptional activity of nuclear factor *kappa* B (NF-κB), and the deregulation of this signaling pathway is a contributor to lymphomagenesis[33]. NF-κB is a primary transcription factor normally sequestered in the cytoplasm[34]. As part of the innate immune response, it is a point of convergence of various pathways that originate on surface receptors, including the BCR, leading to inducible modifications of the expression of genes that modify the immune response, cell survival, proliferation and apoptosis[34]. Deregulation of pathways converging on NF-κB can thus lead to cellular immortalization, and is frequent in immune, autoimmune and oncologic diseases, including MALT lymphoma, where it is fundamental for the continued development of a lymphoma that has achieved *H. pylori*-independence[3,35].

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)[10,36]. MALT1 oligomerizes with BCL10, leading to the downstream activation of NF-κB[10,34,37]. 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 antigenic stimulation[10]. 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[10,38]. 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[31].

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[10]. They generate oncogenic fusion proteins that activate the NF-κB pathway, and lymphomas with these translocations show an overexpression of NF-κB target genes[31,39].

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[10,38]. Therefore, this fusion gene results in a positive feedback cycle that leads to the unregulated, constitutive activation of NF-κB[34]. The API2-MALT1 fusion oncoprotein also contributes to the constitutive activation of NF-κB through an additional alternative non-canonical pathway[33,34]. 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[10,40]. 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[10,39-41]. The NF-κB-activating translocations t(1;14) and t(14;18) have similarly been noted to be associated with bacterial eradication-resistance[39].

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%), colonic and pulmonary locations[12,41,42]. 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[43]. It is absent from non-complicated *H. pylori*-positive gastritis but often found in gastric MALT lymphoma patients infected with CagA-positive *H. pylori*[10]. 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[41,44]. On the other hand, it associates with advanced stages and submucosal involvement, being absent from lymphomas restricted to the mucosa[10,41].

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[10]. 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[45-47].

The t(1;14) (p22;q32) induces the juxtaposition of *BCL10* with the *IGH* gene enhancer region, with a resulting overexpression of BCL10 and activation of NF-κB[38]. 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[10].

The t(3;14) (p14;q32) apposes the *FOXP1* with the *IGH* enhancer, resulting in the overexpression of the former[48]. FOX family proteins have been shown to be involved in signal transduction that mediates proliferation, differentiation and the immune response[49]. 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[48-51]. 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[48].

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[55]. 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[3,54,56-58].

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[12,59,60]. 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), cytogenetics and molecular biology, moreover considering that the histological differential diagnosis between severe gastritis and early stage lymphoma can be difficult[4].

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 monoclonal 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[6,10,18,45]. Pathologic acquired MALT and MALT lymphoma are similar to physiological MALT[18]. 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[10,18,22,65]. 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)[18,45] (Table 3). Immunophenotyping can also contribute to the differential diagnosis between small cell lymphomas[45]. 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[18,45,65]. Malignant cells exhibit light-chain restriction, as a marker of clonality[66]. 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

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

Antigen	Notes
sIg^+	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
$CD23^-$	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[45,51,68]. Transformed MALT/DLBCL appears to have a similar prognosis to *de novo* DLBCL, with overlapping progression-free and overall survivals[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%)[21]. 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[70]. 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[72].

It has been suggested that the use of magnified endoscopy techniques for the evaluation of the microstructural 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].

Table 4 Association between abdominal computerized tomography findings and the likelihood of low-grade and high-grade lesions

Low-grade lesions	High-grade lesions
Normal scans	Abnormal scans
Gastric wall thickening < 5-10 mm	Diffuse gastric wall thickening > 10 mm
Small depressed lesions with vague margins	Well-demarcated masses with homogeneous attenuation and mild contrast enhancement
	Perigastric adenopathies more likely

Adapted from Hayashi *et al*[76], 2010.

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[10]. 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 polypoid masses with homogeneous and isoattenuating or hypoattenuating enhancement[71,75]. 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	Radaszkiewicz	Lugano	Paris
Gastrointestinal tract	I E	I E	I	T^1 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			II	
Adjacent tissues or organs	I E	I E	II E	T4 N0 M0
Regional lymph nodes	II E	II E	II 1	T^1 N1 M0
Infradiaphragmatic distal lymph nodes	II E	II E	II 2	T^1 N2 M0
Disseminated disease			IV	
Supradiaphragmatic lymph nodes	III E	III E	IV	T^1 N3 M0
Non-contiguous gastrointestinal[2]	IV E	IV E	IV	T^1 N^1 M1
Non-contiguous metastasis[3]	IV E	IV E	IV	T^1 N^1 M2
Marrow involvement	IV E	IV E	IV E	T^1 N^1 M^1B1

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 III. [1]Any subtype of tumor extension (T1 to T4) or nodal (N0 to N3) or metastatic (M0 to M2) involvement; [2]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); [3]Including the non-contiguous involvement of the peritoneum. References for the 4 staging systems are given in the main text.

cal of T-cell enteropathy; DLBCL is multiform and often invasive[76]. Despite its utility for initial staging, abdominal CT scanning does not appear to be useful for the follow-up of localized gastric MALT lymphoma[72]. In a series of patients with early-stage gastric MALT lymphoma in complete remission, 5.7% had recurrent disease, which was confined to the mucosa and, therefore, undetectable on CT[72].

Staging

The staging of both Hodgkin and non-Hodgkin lymphoma is standardized through the Ann Arbor system, with the Costwolds modifications[77,78]. Due to the intrinsic limitations of this system in primary extranodal lymphomas of the gastrointestinal tract, the Radaszkiewicz and the Lugano modifications were proposed, with variable success[79,80]. To overcome the perceived shortcomings of the various lymphoma staging system adaptations, both for the correct definition of the primary tumor extension and depth of infiltration, and as a basis for therapeutic decisions, the European Gastro-Intestinal Lymphoma 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).

Table 6 Tumor-node-metastasis staging system qualifiers

	Stage	Definition
Tumor	Tx	Extension of lymphoma not established
	T0	No evidence of primary lymphoma
Nodes	Nx	Nodal involvement not evaluated
	N0	No evidence of nodal involvement
Metastasis	Mx	Dissemination of lymphoma not evaluated
	M0	No evidence of lymphoma dissemination
Bone marrow	Bx	Bone marrow infiltration not evaluated
	B0	No evidence of bone marrow infiltration

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.

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[45]. 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[82] (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

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[82,85,86]. The presence of extragastric disease also appears to have prognostic value[83]. 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[87,88].

Treatment

Current guidelines are consensual in indicating *H. pylori* eradication therapy as the first line approach in gastric MALT lymphoma[89]. 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[65,89]. Therefore, different centers report a variety of approaches, many of which have relevant side-effects[8,57,90].

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[45,90-92]. Second remissions can be regained with retreatment; however, the disease-free interval tends to decrease after each subsequent remission[91]. Early-stage disease tends to remain localized for a long time, and responds satisfactory to local treatment approaches, such as surgery or radiotherapy[90]. 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[90].

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[93,94].

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[10,95-99]. 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[4]. Nevertheless, when these methods are available, testing for t(11;18) could be a helpful *a priori* predictor of response to therapy[65,100].

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[101]. 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[102]. PPI should be suspended at least one week before testing[101]. 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"[65].

The first line therapy for eradication is the triple association between a PPI, clarithromycin and either metronidazole or amoxicillin[65,101]. In special select cases, the antibiotics may have to be selected through an antibiotic sensitivity test, as in the case of known antibiotic allergies[103]. 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[101]. 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[104]. In the case of treatment failure, eradication should be re-attempted with a quadruple association of a PPI, tetracycline, metronidazole and a bismuth salt[101].

While over 80% of patients can achieve a complete lymphoma remission (according to GELA criteria[105]) 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[97,106]. 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

Table 8 Chemotherapy treatment options in American and European guidelines

Drug group	Drugs
Alkylators	Chlorambucil[1]
	Cyclophosphamide[1,2]
	Bendamustine[1,2]
Purine nucleoside analogues	Fludarabine[1,2]
	Cladribine[1]
Anthracyclines and anthracenediones	Doxorubicin[2]
	Mitoxantrone[2]
Vinca alkaloids	Vincristine[2]

Reflecting the lack of clear consensus, current guidelines propose different associations of these agents as monotherapy, combination chemotherapy, and combined immunochemotherapy with rituximab. [1]European Society for Medical Oncology 2013 guidelines; [2]National Comprehensive Cancer Network 2011 guidelines.

component size; significantly, complete remissions were achieved in over 98% of distal tumors, but only in 70% of proximal tumors[99].

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[4,10]. 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[107]. 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[106,108]. Nevertheless, the ideal duration of the follow-up period after initial eradication treatment remains to be defined, with some authors suggesting immediate treatment after a successful eradication without lymphoma remission, while others propose continued watchful waiting[97]. 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[109].

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[72]. 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[72]. 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[98,107,108].

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[110,111].

Local treatment approaches: In gastric MALT lymphoma, the current view is towards stomach-conserving conservative treatment, avoiding first-line surgical resection[98]. 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[61,112,113]. 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[58,98,106,114].

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[4,8,115].

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[65,116]. 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[117].

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[27]. Fludarabine demonstrated a significant reduction in peripheral blood T-cells, compared to eradication alone, while in biopsy samples there was an increase in T_{regs}[27]. Cladribine achieved a complete response rate of 100% in primary gastric lymphomas, with an overall (gastric and extragastric) survival at 80 mo of 84%[118]. 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[90]. A phase Ⅱ trial of gemcitabine, a less T-suppressive analogue expected to overcome this problem, was discontinued due to disappointing results[90].

Single-agent alkylators, including chlorambucil and bendamustine, have shown clinical effectiveness with acceptable toxicity, demonstrating that this is another valid treatment approach[91,115,119,120]. However, it has been suggested that t(11;18) is a marker of non-response to alkylating regimens[65].

Several of the newer agents have also been tried in gastric MALT lymphomas. Thalidomide is an antiangiogenic and immunomodulatory drug with anti-NF-κB activity, which justifies its potential utility in MALT lymphomas[35]. 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-κB in residual neoplastic cells and tumor microenvironment[35]. These data suggest that the presence of t(11;18) is also predictive of non-response to thalidomide[35].

The role of the ubiquitin proteasome system (UPS) in the regulation of the NF-κB pathway serves as the rationale behind the use of proteasome inhibitors in the treatment of MALT lymphomas[121]. Previous basic and clinical experience with these agents has demonstrated that they disrupt multiple UPS-dependent cellular pathways, with apoptosis as the final event[8]. 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%[8,121]. 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[8].

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[122-125]. 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[71,91,126-128]. 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[7,129].

An alternative to rituximab is radio-immunotherapy with ^{90}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[130,131].

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.

REFERENCES

1 **Isaacson P**, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer* 1983; **52**: 1410-1416 [PMID: 6193858 DOI: 10.1002/1097-0142(19831015)52::8<1410::AID-CNCR2820520813>3.0.CO;2-3]

2 **Isaacson P**, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984; **53**: 2515-2524 [PMID: 6424928]

3 **Sagaert X**, Van Cutsem E, De Hertogh G, Geboes K, Tousseyn T. Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 336-346 [PMID: 20440281 DOI: 10.1038/nrgastro.2010.58]

4 **Owens SR**, Smith LB. Molecular Aspects of H. pylori-Related MALT Lymphoma. *Patholog Res Int* 2011; **2011**: 193149 [PMID: 21318155]

5 **Swerdlow SH**, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer (IARC); 2008. Available from: URL: http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4002

6 **Powell LD**, Baum LG. Overview and compartmentalization of the immune system. In: Hoffman R, Furie B, McGlave P, Silberstein LE, Shattil SJ, Benz EJ, Heslop H. Hematology: Basic Principles and Practice. Oxford, UK: Churchill Livingstone, 2008

7 **Orciuolo E**, Buda G, Sordi E, Baraté C, Galimberti S, Ciancia E, Petrini M. 2CdA chemotherapy and rituximab in the treatment of marginal zone lymphoma. *Leuk Res* 2010; **34**: 184-189 [PMID: 19414190 DOI: 10.1016/j.leukres.2009.04.003]

8 **Troch M**, Jonak C, Müllauer L, Püspök A, Formanek M, Hauff W, Zielinski CC, Chott A, Raderer M. A phase II study of bortezomib in patients with MALT lymphoma. *Haematologica* 2009; **94**: 738-742 [PMID: 19336742 DOI: 10.3324/haematol.2008.001537]

9 **Kim do Y**, Kim YS, Huh HJ, Choi JS, Yeo JS, Kwak BS, Chae SL. A case of monoclonal gammopathy in extranodal marginal zone B-cell lymphoma of the small intestine. *Korean J Lab Med* 2011; **31**: 18-21 [PMID: 21239866 DOI: 10.3343/kjlm.2011.31.1.18]

10 **Isaacson PG**. Update on MALT lymphomas. *Best Pract Res Clin Haematol* 2005; **18**: 57-68 [PMID: 15694184 DOI: 10.1016/j.beha.2004.08.003]

11 **Craig VJ**, Cogliatti SB, Arnold I, Gerke C, Balandat JE, Wündisch T, Müller A. B-cell receptor signaling and CD40 ligand-independent T cell help cooperate in Helicobacter-induced MALT lymphomagenesis. *Leukemia* 2010; **24**: 1186-1196 [PMID: 20428202 DOI: 10.1038/leu.2010.76]

12 **Konoplev S**, Lin P, Qiu X, Medeiros LJ, Yin CC. Clonal relationship of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue involving different sites. *Am J Clin Pathol* 2010; **134**: 112-118 [PMID: 20551275 DOI: 10.1309/AJCP0HT6ZGSZKNFT]

13 **Craig VJ**, Arnold I, Gerke C, Huynh MQ, Wündisch T, Neubauer A, Renner C, Falkow S, Müller A. Gastric MALT lymphoma B cells express polyreactive, somatically mutated immunoglobulins. *Blood* 2010; **115**: 581-591 [PMID: 19965661 DOI: 10.1182/blood-2009-06-228015]

14 **Hoogeboom R**, Bende RJ, van Noesel CJ. MALT lymphoma-derived rheumatoid factors are nonpolyreactive high-affinity antibodies. *Blood* 2010; **116**: 1818-1819; author reply 1819-1820 [PMID: 20829382 DOI: 10.1182/blood-2010-03-274613]

15 **García M**, Bellosillo B, Sánchez-González B, García-Payarols F, Seoane A, Ferrer AM, Gimeno E, Barranco LE, Torner A, Solé F, Besses C, Serrano S, Salar A. Study of regulatory T-cells in patients with gastric malt lymphoma: influence on treatment response and outcome. *PLoS One* 2012; **7**: e51681 [PMID: 23284739 DOI: 10.1371/journal.pone.0051681]

16 **Bergman MP**, D'Elios MM. Cytotoxic T cells in H. pylori-related gastric autoimmunity and gastric lymphoma. *J Biomed Biotechnol* 2010; **2010**: 104918 [PMID: 20617132]

17 **Mégraud F**. Helicobacter pylori infection: Review and practice. *Presse Med* 2010; **39**: 815-822 [PMID: 20627443 DOI: 10.1016/j.lpm.2010.04.004]

18 **Eck M**, Fischbach W. Gastric MALT-type lymphoma. Pathology, pathogenesis, diagnostics and therapy. *Pathologe* 2010; **31**: 188-194 [PMID: 20349062 DOI: 10.1007/s00292-009-1269-2]

19 **Bhandari A**, Crowe SE. Helicobacter pylori in gastric malignancies. *Curr Gastroenterol Rep* 2012; **14**: 489-496 [PMID: 23054813 DOI: 10.1007/s11894-012-0296-y]

20 **Siddiqui ST**, Naz E, Danish F, Mirza T, Aziz S, Ali A. Frequency of Helicobacter pylori in biopsy proven gastritis and its association with lymphoid follicle formation. *J Pak Med Assoc* 2011; **61**: 138-141 [PMID: 21375161]

21 **Pervez S**, Ali N, Aaqil H, Mumtaz K, Siddiq Ullah S, Akhtar N. Gastric MALT lymphoma: a rarity. *J Coll Physicians Surg Pak* 2011; **21**: 171-172 [PMID: 21419026]

22 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176 [PMID: 1682595 DOI: 10.1016/0140-6736(91)92035-Z]

23 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

24 **Nakamura S**, Aoyagi K, Furuse M, Suekane H, Matsumoto T, Yao T, Sakai Y, Fuchigami T, Yamamoto I, Tsuneyoshi M, Fujishima M. B-cell monoclonality precedes the development of gastric MALT lymphoma in Helicobacter pylori-associated chronic gastritis. *Am J Pathol* 1998; **152**: 1271-1279 [PMID: 9588895]

25 **Kang SY**, Han JH, Ahn MS, Lee HW, Jeong SH, Park JS, Cho YK, Han SU, Kim YB, Kim JH, Sheen SS, Lim HY, Choi JH. Helicobacter pylori infection as an independent prognostic factor for locally advanced gastric cancer patients treated with adjuvant chemotherapy after curative resection. *Int J Cancer* 2012; **130**: 948-958 [PMID: 21425257 DOI: 10.1002/ijc.26081]

26 **Hussell T**, Isaacson PG, Crabtree JE, Spencer J. Helicobacter pylori-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *J Pathol* 1996; **178**: 122-127 [PMID: 8683376 DOI: 10.1002/(SICI)1096-9896(199602)178::2<122::AID-PATH486>3.0.CO;2-D]

27 **de Boer JP**, Raderer M, van Tinteren H, Aleman BM, Boot H, de Jong D. Treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with fludarabine: effect on tumor microenvironment. *Leuk Lymphoma* 2011; **52**: 2262-2269 [PMID: 21848361 DOI: 10.3109/10428194.2011.607527]

28 **Hatakeyama M**, Higashi H. Helicobacter pylori CagA: a new paradigm for bacterial carcinogenesis. *Cancer Sci* 2005; **96**: 835-843 [PMID: 16367902 DOI: 10.1111/j.1349-7006.2005.00130.x]

29 **Li SP**, Chen XJ, Sun AH, Zhao JF, Yan J. CagA(+) H. pylori induces Akt1 phosphorylation and inhibits transcription of p21(WAF1/CIP1) and p27(KIP1) via PI3K/Akt1 pathway. *Biomed Environ Sci* 2010; **23**: 273-278 [PMID: 20934114 DOI: 10.1016/S0895-3988(10)60063-3]

30 **Nitta H**, Zhang W, Kelly BD, Miller M, Pestic-Dragovich L, Bieniarz C, Vasicek TJ, Marafioti T, Rimsza L, Grogan TM. Automated brightfield break-apart in situ hybridization (ba-ISH) application: ALK and MALT1 genes as models. *Methods* 2010; **52**: 352-358 [PMID: 20621192 DOI: 10.1016/j.ymeth.2010.07.005]

31 **Du MQ**. MALT lymphoma: many roads lead to nuclear factor-κb activation. *Histopathology* 2011; **58**: 26-38 [PMID: 21261681 DOI: 10.1111/j.1365-2559.2010.03699.x]

32 **González D**, van der Burg M, García-Sanz R, Fenton JA, Langerak AW, González M, van Dongen JJ, San Miguel JF, Morgan GJ. Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma. *Blood* 2007; **110**: 3112-3121 [PMID: 17634408 DOI: 10.1182/blood-2007-02-069625]

33 **Rosebeck S**, Madden L, Jin X, Gu S, Apel IJ, Appert A, Hamoudi RA, Noels H, Sagaert X, Van Loo P, Baens M, Du MQ, Lucas PC, McAllister-Lucas LM. Cleavage of NIK by the API2-MALT1 fusion oncoprotein leads to noncanonical NF-kappaB activation. *Science* 2011; **331**: 468-472 [PMID: 21273489 DOI: 10.1126/science.1198946]

34 **Nishikori M**. Classical and alternative NF-kB activation pathways and their roles in lymphoid malignancies. *J Clin Exp Hematopathol* 2005; **45**: 15-24 [DOI: 10.3960/jslrt.45.15]

35 **Kuo SH**, Cheng AL, Lin CW, Hsu CH, Wu MS, Yeh KH, Tzeng YS, Chen LT. t(11; 18)(q21; q21) translocation as predictive marker for non-responsiveness to salvage thalidomide therapy in patients with marginal zone B-cell lymphoma with gastric involvement. *Cancer Chemother Pharmacol* 2011; **68**: 1387-1395 [PMID: 21465313 DOI: 10.1007/s00280-011-1631-y]

36 **Dong G**, Liu C, Ye H, Gong L, Zheng J, Li M, Huang X, Huang X, Huang Y, Shi Y, Yin W, Gao Z. BCL10 nuclear expression and t(11; 18)(q21; q21) indicate nonresponsiveness to Helicobacter pylori eradication of Chinese primary gastric MALT lymphoma. *Int J Hematol* 2008; **88**: 516-523 [PMID: 18949449 DOI: 10.1007/s12185-008-0187-z]

37 **McAllister-Lucas LM**, Baens M, Lucas PC. MALT1 protease: a new therapeutic target in B lymphoma and beyond? *Clin Cancer Res* 2011; **17**: 6623-6631 [PMID: 21868762 DOI: 10.1158/1078-0432.CCR-11-0467]

38 **Nakagawa M**, Hosokawa Y, Yonezumi M, Izumiyama K, Suzuki R, Tsuzuki S, Asaka M, Seto M. MALT1 contains nuclear export signals and regulates cytoplasmic localization of BCL10. *Blood* 2005; **106**: 4210-4216 [PMID: 16123224 DOI: 10.1182/blood-2004-12-4785]

39 **Hamoudi RA**, Appert A, Ye H, Ruskone-Fourmestraux A, Streubel B, Chott A, Raderer M, Gong L, Wlodarska I, De Wolf-Peeters C, MacLennan KA, de Leval L, Isaacson PG, Du MQ. Differential expression of NF-kappaB target genes in MALT lymphoma with and without chromosome translocation: insights into molecular mechanism. *Leukemia* 2010; **24**: 1487-1497 [PMID: 20520640 DOI: 10.1038/leu.2010.118]

40 **Bende RJ**, Aarts WM, Riedl RG, de Jong D, Pals ST, van Noesel CJ. Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity. *J Exp Med* 2005; **201**: 1229-1241 [PMID: 15837810 DOI: 10.1084/jem.20050068]

41 **Nakamura S**, Matsumoto T, Nakamura S, Jo Y, Fujisawa K, Suekane H, Yao T, Tsuneyoshi M, Iida M. Chromosomal translocation t(11; 18)(q21; q21) in gastrointestinal mucosa associated lymphoid tissue lymphoma. *J Clin Pathol* 2003; **56**: 36-42 [PMID: 12499431 DOI: 10.1136/jcp.56.1.36]

42 **Tibiletti MG**, Milani K, Martin V, Zucca E, Motta T, Cortelazzo S, Pinotti G, Mazzucchelli L, Pruneri G, Martinelli G, Barbazza R, Capella C, Bertoni F. Chromosome instability and translocation t(11; 18) in primary gastric marginal zone B-cell lymphoma of MALT-type. *Hematol Oncol* 2007; **25**: 184-188 [PMID: 17607663 DOI: 10.1002/hon.825]

43 **Maes B**, Baens M, Marynen P, De Wolf-Peeters C. The product of the t(11; 18), an API2-MLT fusion, is an almost exclusive finding in marginal zone cell lymphoma of extranodal MALT-type. *Ann Oncol* 2000; **11**: 521-526 [PMID: 10907943 DOI: 10.1023/A:1008357314157]

44 **Li BZ**, Lu HF, Zhou XY, Yang WT, Kong YY, Fan YZ, Shi DR. Frequency of genetic aberrations in mucosa-associated lymphoid tissue lymphoma of different sites. *Zhonghua Binglixue Zazhi* 2008; **37**: 604-608 [PMID: 19094584]

45 **Jaffe ES**, Pittaluga S. The pathologic basis for the classification of non-Hodgkin lymphomas. In: Hoffman R, Furie B, McGlave P, Silberstein LE, Shattil SJ, Benz EJ, Heslop H. Hematology: Basic Principles and Practice. Oxford, UK: Churchill Livingstone, 2008

46 **Streubel B**, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, Raderer M, Chott A. T(14; 18)(q32; q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003; **101**: 2335-2339 [PMID: 12406890 DOI: 10.1182/blood-2002-09-2963]

47 **Sanchez-Izquierdo D**, Buchonnet G, Siebert R, Gascoyne RD, Climent J, Karran L, Marin M, Blesa D, Horsman D, Rosenwald A, Staudt LM, Albertson DG, Du MQ, Ye H, Marynen P, Garcia-Conde J, Pinkel D, Dyer MJ, Martinez-Climent JA. MALT1 is deregulated by both chromosomal translocation and amplification in B-cell non-Hodgkin lymphoma. *Blood* 2003; **101**: 4539-4546 [PMID: 12560219 DOI: 10.1182/blood-2002-10-3236]

48 **Streubel B**, Vinatzer U, Lamprecht A, Raderer M, Chott A. T(3; 14)(p14.1; q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. *Leukemia* 2005; **19**: 652-658 [PMID: 15703784 DOI: 10.1038/sj.leu.2403644]

49 **Sagaert X**, de Paepe P, Libbrecht L, Vanhentenrijk V, Verhoef G, Thomas J, Wlodarska I, De Wolf-Peeters C. Forkhead box protein P1 expression in mucosa-associated lymphoid tissue lymphomas predicts poor prognosis and transformation to diffuse large B-cell lymphoma. *J Clin Oncol* 2006; **24**: 2490-2497 [PMID: 16636337 DOI: 10.1200/JCO.2006.05.6150]

50 **Zhai L**, Zhao Y, Ye S, Huang H, Tian Y, Wu Q, Lin H, Lin T. Expression of PIK3CA and FOXP1 in gastric and intestinal non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue type. *Tumour Biol* 2011; **32**: 913-920 [PMID: 21660567 DOI: 10.1007/s13277-011-0192-3]

51 **Craig VJ**, Cogliatti SB, Imig J, Renner C, Neuenschwander S, Rehrauer H, Schlapbach R, Dirnhofer S, Tzankov A, Müller A. Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. *Blood* 2011; **117**: 6227-6236 [PMID: 21460242 DOI: 10.1182/blood-2010-10-312231]

52 **Zhang XM**, Zhang WY, Zhou YP, Mo XL, Li YP, Wang GQ, Zhou YQ, Zeng SE, Li GD, Ye HT. Study on genetic aberrations of ocular mucosa-associated lymphoid tissue lymphomas occurring in southern China. *Zhonghua Binglixue Zazhi* 2010; **39**: 513-517 [PMID: 21055028]

53 **Remstein ED**, Dogan A, Einerson RR, Paternoster SF, Fink SR, Law M, Dewald GW, Kurtin PJ. The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. *Am J Surg Pathol* 2006; **30**: 1546-1553 [PMID: 17122510 DOI: 10.1097/01.pas.0000213275.60962.2a]

54 **Thieblemont C**, Berger F, Dumontet C, Moullet I, Bouafia F, Felman P, Salles G, Coiffier B. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000; **95**: 802-806 [PMID: 10648389]

55 **He S**, Guo Y, Bei CF, Dai YZ, Zhu DB, Li CS, Zhu XH, LE MZ. Gastrointestinal B-cell lymphoma: a morphologic and immunohistochemical study of 194 cases. *Zhonghua Binglixue Zazhi* 2010; **39**: 814-818 [PMID: 21215096]

56 **Samee A**, Rukin N, Siddiqui I, Halliday M, Farmer M. A solitary rectal mucosa-associated lymphoid tissue (MALT) lymphoma. *BMJ Case Rep* 2010; **2010**: pii: bcr0120102649 [PMID: 22767556 DOI: 10.1136/bcr.01.2010.2649]

57 **Ersoz F**, Toros AB, Bektas H, Ozcan O, Koc O, Arikan S. MALT lymphoma of the rectum, presenting with rectal prolapsus: a case report. *Cases J* 2010; **3**: 33 [PMID: 20180989 DOI: 10.1186/1757-1626-3-33]

58 **Aleman BM**, Haas RL, van der Maazen RW. Role of radio-

therapy in the treatment of lymphomas of the gastrointestinal tract. *Best Pract Res Clin Gastroenterol* 2010; **24**: 27-34 [PMID: 20206106 DOI: 10.1016/j.bpg.2009.12.002]
59 **Dolak W**, Raderer M, Maresch J, Muellauer L, Puespoek A, Chott A, Haefner M. Detection of gastric MALT lymphoma spreading to the small bowel by enteroscopy. *Endoscopy* 2011; **43**: 731-733 [PMID: 21656457 DOI: 10.1055/s-0030-1256435]
60 **Matsuo T**, Ichimura K, Okada H, Shinagawa K, Fukushima K, Okano M, Otsuka M, Yoshino T. Clonal analysis of bilateral, recurrent, or systemically multifocal ocular adnexal lymphoma. *J Clin Exp Hematop* 2010; **50**: 27-38 [PMID: 20505273 DOI: 10.3960/jslrt.50.27]
61 **Devi P**, Pattanayak L, Samantaray S. Synchronous adenocarcinoma and mucosa-associated lymphoid tissue lymphoma of the colon. *Saudi J Gastroenterol* 2011; **17**: 69-71 [PMID: 21196657 DOI: 10.4103/1319-3767.74455]
62 **Akiba J**, Nakane T, Arakawa F, Ohshima K, Yano H. Collision of EBV-associated gastric carcinoma and primary gastric extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the remnant stomach. *Pathol Int* 2010; **60**: 102-106 [PMID: 20398194 DOI: 10.1111/j.1440-1827.2009.02479.x]
63 **Terada T**. One patient with double lymphomas: simultaneous gastric MALT lymphoma and ileal diffuse large B-cell lymphoma. *Int J Clin Exp Pathol* 2012; **5**: 260-263 [PMID: 22558482]
64 **Melo GM**, Sguilar DA, Petiti CM, Eichstaedt AG, Caiado RR, Souza RA. Concomitant thyroid Malt lymphoma and papillary thyroid carcinoma. *Arq Bras Endocrinol Metabol* 2010; **54**: 425-428 [PMID: 20625656]
65 **Dreyling M**, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, Kluin-Nelemans JC, Ladetto M, Le Gouill S, Iannitto E, Pileri S, Rodriguez J, Schmitz N, Wotherspoon A, Zinzani P, Zucca E. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol* 2013; **24**: 857-877 [PMID: 23425945 DOI: 10.1093/annonc/mds643]
66 **Borie R**, Wislez M, Antoine M, Fleury-Feith J, Thabut G, Crestani B, Monnet I, Nunes H, Delfau-Larue MH, Cadranel J. Clonality and phenotyping analysis of alveolar lymphocytes is suggestive of pulmonary MALT lymphoma. *Respir Med* 2011; **105**: 1231-1237 [PMID: 21481576 DOI: 10.1016/j.rmed.2011.03.018]
67 **Thorns C**, Kuba J, Bernard V, Senft A, Szymczak S, Feller AC, Bernd HW. Deregulation of a distinct set of microRNAs is associated with transformation of gastritis into MALT lymphoma. *Virchows Arch* 2012; **460**: 371-377 [PMID: 22395483 DOI: 10.1007/s00428-012-1215-1]
68 **Ferrucci PF**, Zucca E. Primary gastric lymphoma pathogenesis and treatment: what has changed over the past 10 years? *Br J Haematol* 2007; **136**: 521-538 [PMID: 17156403 DOI: 10.1111/j.1365-2141.2006.06444.x]
69 **Li X**, Xia B, Guo S, Zhan Z, Zhang L, Zhao D, Wu X, Zhang Y. A retrospective analysis of primary gastric diffuse large B-cell lymphoma with or without concomitant mucosa-associated lymphoid tissue (MALT) lymphoma components. *Ann Hematol* 2013; **92**: 807-815 [PMID: 23417758 DOI: 10.1007/s00277-013-1701-9]
70 **Ishimaru A**, Kitsukawa M. Report of a case of perforated giant gastric malignant lymphoma. *Gan To Kagaku Ryoho* 2011; **38**: 663-666 [PMID: 21499001]
71 **Ikuta K**, Fujiya M, Ueno N, Hosoki T, Moriichi K, Honda M, Torimoto Y, Yamochi T, Ota H, Kohgo Y. Atypical mucosa-associated lymphoid tissue lymphoma in the transverse colon associated with macroglobulinemia. *Intern Med* 2010; **49**: 677-682 [PMID: 20371958 DOI: 10.2169/internalmedicine.49.3160]
72 **Choi JY**, Lee GH, Ahn JY, Kim MY, Lee JH, Choi KS, Kim do H, Choi KD, Song HJ, Jung HY, Kim JH. The role of abdominal CT scan as follow-up after complete remission with successful Helicobacter pylori eradication in patients with H. pylori-positive stage I(E1) gastric MALT lymphoma. *Helicobacter* 2011; **16**: 36-41 [PMID: 21241410 DOI: 10.1111/j.1523-5378.2010.00807.x]
73 **Ono S**, Kato M, Ono Y, Nishida U, Yamamoto K, Shimizu Y, Asaka M. Target biopsy using magnifying endoscopy in clinical management of gastric mucosa-associated lymphoid tissue lymphoma. *J Gastroenterol Hepatol* 2011; **26**: 1133-1138 [PMID: 21443666 DOI: 10.1111/j.1440-1746.2011.06729.x]
74 **Bahn YE**, Lee SK, Kwon SY, Kim SP. Sonographic appearances of mucosa-associated lymphoid tissue lymphoma of the submandibular gland confirmed with sonographically guided core needle biopsy. *J Clin Ultrasound* 2011; **39**: 228-232 [PMID: 21480289 DOI: 10.1002/jcu.20754]
75 **Kim HJ**, Ha HK, Kim HJ, Byeon JS, Kim MJ, Lee SS, Park SH, Kim AY. Gastrointestinal dissemination of mucosa-associated lymphoid tissue lymphoma: computed tomographic findings. *J Comput Assist Tomogr* 2010; **34**: 187-192 [PMID: 20351501 DOI: 10.1097/RCT.0b013e3181bbd21e]
76 **Hayashi D**, Devenney-Cakir B, Lee JC, Kim SH, Cheng J, Goldfeder S, Choi BI, Guermazi A. Mucosa-associated lymphoid tissue lymphoma: multimodality imaging and histopathologic correlation. *AJR Am J Roentgenol* 2010; **195**: W105-W117 [PMID: 20651169 DOI: 10.2214/AJR.09.4105]
77 **Carbone PP**, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971; **31**: 1860-1861 [PMID: 5121694]
78 **Lister TA**, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, Rosenberg SA, Coltman CA, Tubiana M. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; **7**: 1630-1636 [PMID: 2809679]
79 **Radaszkiewicz T**, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. *Gastroenterology* 1992; **102**: 1628-1638 [PMID: 1568573]
80 **Rohatiner A**, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, Lister TA, Norton A, Salem P, Shipp M. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol* 1994; **5**: 397-400 [PMID: 8075046]
81 **Ruskoné-Fourmestraux A**, Dragosics B, Morgner A, Wotherspoon A, De Jong D. Paris staging system for primary gastrointestinal lymphomas. *Gut* 2003; **52**: 912-913 [PMID: 12740354 DOI: 10.1136/gut.52.6.912]
82 A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; **329**: 987-994 [PMID: 8141877 DOI: 10.1056/NEJM199309303291402]
83 **Troch M**, Wöhrer S, Raderer M. Assessment of the prognostic indices IPI and FLIPI in patients with mucosa-associated lymphoid tissue lymphoma. *Anticancer Res* 2010; **30**: 635-639 [PMID: 20332482]
84 **Heilgeist A**, McClanahan F, Ho AD, Witzens-Harig M. Prognostic value of the Follicular Lymphoma International Prognostic Index score in marginal zone lymphoma: an analysis of clinical presentation and outcome in 144 patients. *Cancer* 2013; **119**: 99-106 [PMID: 22736411 DOI: 10.1002/cncr.27704]
85 **Olszewski AJ**, Castillo JJ. Survival of patients with marginal zone lymphoma: analysis of the Surveillance, Epidemiology, and End Results database. *Cancer* 2013; **119**: 629-638 [PMID: 22893605 DOI: 10.1002/cncr.27773]
86 **Todorovic M**, Balint B, Jevtic M, Suvajdzic N, Ceric A, Stamatovic D, Markovic O, Perunicic M, Marjanovic S, Krstic M. Primary gastric mucosa associated lymphoid tissue lymphoma: clinical data predicted treatment outcome. *World J Gastroenterol* 2008; **14**: 2388-2393 [PMID: 18416467 DOI: 10.3748/wjg.14.2388]

87 **Flossbach L**, Antoneag E, Buck M, Siebert R, Mattfeldt T, Möller P, Barth TF. BCL6 gene rearrangement and protein expression are associated with large cell presentation of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Int J Cancer* 2011; **129**: 70-77 [PMID: 20830719 DOI: 10.1002/ijc.25663]

88 **Chen YW**, Hu XT, Liang AC, Au WY, So CC, Wong ML, Shen L, Tao Q, Chu KM, Kwong YL, Liang RH, Srivastava G. High BCL6 expression predicts better prognosis, independent of BCL6 translocation status, translocation partner, or BCL6-deregulating mutations, in gastric lymphoma. *Blood* 2006; **108**: 2373-2383 [PMID: 16772602 DOI: 10.1182/blood-2006-05-022517]

89 **Ruskoné-Fourmestraux A**, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, Montalban C, Raderer M, Savio A, Wotherspoon A. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut* 2011; **60**: 747-758 [PMID: 21317175 DOI: 10.1136/gut.2010.224949]

90 **Oh SY**, Kim WS, Lee DH, Kim SJ, Kim SH, Ryoo BY, Kang HJ, Choi YJ, Chung JS, Kim HJ, Suh C. Phase II study of gemcitabine for treatment of patients with advanced stage marginal zone B-cell lymphoma: Consortium for Improving Survival of Lymphoma (CISL) trial. *Invest New Drugs* 2010; **28**: 171-177 [PMID: 19421710 DOI: 10.1007/s10637-009-9260-6]

91 **Kirschbaum M**, Frankel P, Popplewell L, Zain J, Delioukina M, Pullarkat V, Matsuoka D, Pulone B, Rotter AJ, Espinoza-Delgado I, Nademanee A, Forman SJ, Gandara D, Newman E. Phase II study of vorinostat for treatment of relapsed or refractory indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol* 2011; **29**: 1198-1203 [PMID: 21300924 DOI: 10.1200/JCO.2010.32.1398]

92 **Nakamura S**, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, Tari A, Kitadai Y, Matsumoto H, Nagaya T, Kamoshida T, Watanabe N, Chiba T, Origasa H, Asaka M. Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. *Gut* 2012; **61**: 507-513 [PMID: 21890816 DOI: 10.1136/gutjnl-2011-300495]

93 **Sato C**, Suzuki H, Watanabe M, Kojima K, Tsuchida F, Takeda H. Spontaneous regression of mucosa-associated lymphoid tissue lymphoma of the lung. *Nihon Kokyuki Gakkai Zasshi* 2010; **48**: 677-682 [PMID: 20954370]

94 **Makino Y**, Suzuki H, Nishizawa T, Kameyama K, Hisamatsu T, Imaeda H, Mukai M, Hibi T. Ileal Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma with a Large-Cell Component That Regressed Spontaneously. *Gut Liver* 2010; **4**: 117-121 [PMID: 20479924 DOI: 10.5009/gnl.2010.4.1.117]

95 **Al Furaikh SS**. Remission of high-grade B-cell lymphoma in a pediatric patient following Helicobacter pylori eradication. *Pediatr Int* 2011; **53**: 105-107 [PMID: 21342336 DOI: 10.1111/j.1442-200X.2010.03142.x]

96 **Kuo SH**, Yeh KH, Wu MS, Lin CW, Hsu PN, Wang HP, Chen LT, Cheng AL. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas. *Blood* 2012; **119**: 4838-4844; quiz 5057 [PMID: 22403257 DOI: 10.1182/blood-2012-01-404194]

97 **Suzuki H**, Saito Y, Hibi T. Helicobacter pylori and Gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma: Updated Review of Clinical Outcomes and the Molecular Pathogenesis. *Gut Liver* 2009; **3**: 81-87 [PMID: 20431728 DOI: 10.5009/gnl.2009.3.2.81]

98 **Fischbach W**. Long-term follow-up of gastric lymphoma after stomach conserving treatment. *Best Pract Res Clin Gastroenterol* 2010; **24**: 71-77 [PMID: 20206110 DOI: 10.1016/j.bpg.2009.12.005]

99 **Kim SJ**, Yang S, Min BH, Lee JH, Rhee PL, Rhee JC, Kim JJ. Helicobacter pylori eradication for stage I(E_1) gastric mucosa-associated lymphoid tissue lymphoma: predictive factors of complete remission. *Korean J Gastroenterol* 2010; **55**: 94-99 [PMID: 20168055 DOI: 10.4166/kjg.2010.55.2.94]

100 **Yepes S**, Torres MM, Saavedra C, Andrade R. Gastric mucosa-associated lymphoid tissue lymphomas and Helicobacter pylori infection: a Colombian perspective. *World J Gastroenterol* 2012; **18**: 685-691 [PMID: 22363141 DOI: 10.3748/wjg.v18.i7.685]

101 **Bytzer P**, Dahlerup JF, Eriksen JR, Jarbøl DE, Rosenstock S, Wildt S. Diagnosis and treatment of Helicobacter pylori infection. *Dan Med Bull* 2011; **58**: C4271 [PMID: 21466771]

102 **Suhaila N**, Hussin S, Rahman MM. Comparative efficacy sensitivity and specificity of the tests used for the Diagnosis of Helicobacter pylori. *Pak J Biol Sci* 2010; **13**: 1057-1061 [PMID: 21313878 DOI: 10.3923/pjbs.2010.1057.1061]

103 **Konno T**, Motoori S, Iwamoto N, Miyazawa T, Saito S, Kitagawa N, Saisho H, Furuse J, Itabashi M. A case of mucosa-associated lymphoid tissue lymphoma with penicillin allergy successfully treated with levofloxacin, minomycin and rabeprazole. *Gan To Kagaku Ryoho* 2010; **37**: 1961-1964 [PMID: 20948264]

104 **Medeiros JA**, Gonçalves TM, Boyanova L, Pereira MI, de Carvalho JN, Pereira AM, Cabrita AM. Evaluation of Helicobacter pylori eradication by triple therapy plus Lactobacillus acidophilus compared to triple therapy alone. *Eur J Clin Microbiol Infect Dis* 2011; **30**: 555-559 [PMID: 21207091 DOI: 10.1007/s10096-010-1119-4]

105 **Copie-Bergman C**, Wotherspoon AC, Capella C, Motta T, Pedrinis E, Pileri SA, Bertoni F, Conconi A, Zucca E, Ponzoni M, Ferreri AJ. Gela histological scoring system for post-treatment biopsies of patients with gastric MALT lymphoma is feasible and reliable in routine practice. *Br J Haematol* 2013; **160**: 47-52 [PMID: 23043300 DOI: 10.1111/bjh.12078]

106 **Ono S**, Kato M, Takagi K, Kodaira J, Kubota K, Matsuno Y, Komatsu Y, Asaka M. Long-term treatment of localized gastric marginal zone B-cell mucosa associated lymphoid tissue lymphoma including incidence of metachronous gastric cancer. *J Gastroenterol Hepatol* 2010; **25**: 804-809 [PMID: 20492338 DOI: 10.1111/j.1440-1746.2009.06204.x]

107 **Fischbach W**, Goebeler ME, Ruskone-Fourmestraux A, Wündisch T, Neubauer A, Raderer M, Savio A. Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of Helicobacter pylori can be managed safely by a watch and wait strategy: experience from a large international series. *Gut* 2007; **56**: 1685-1687 [PMID: 17639089 DOI: 10.1136/gut.2006.096420]

108 **Wündisch T**, Dieckhoff P, Greene B, Thiede C, Wilhelm C, Stolte M, Neubauer A. Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by Helicobacter pylori eradication and followed for 10 years. *Gastroenterology* 2012; **143**: 936-942; quiz e13-e14 [PMID: 22750463 DOI: 10.1053/j.gastro.2012.06.035]

109 **Ferreri AJ**, Dolcetti R, Du MQ, Doglioni C, Resti AG, Politi LS, De Conciliis C, Radford J, Bertoni F, Zucca E, Cavalli F, Ponzoni M. Ocular adnexal MALT lymphoma: an intriguing model for antigen-driven lymphomagenesis and microbial-targeted therapy. *Ann Oncol* 2008; **19**: 835-846 [PMID: 17986622 DOI: 10.1093/annonc/mdm513]

110 **Park HS**, Kim YJ, Yang WI, Suh CO, Lee YC. Treatment outcome of localized Helicobacter pylori-negative low-grade gastric MALT lymphoma. *World J Gastroenterol* 2010; **16**: 2158-2162 [PMID: 20440857 DOI: 10.3748/wjg.v16.i17.2158]

111 **Asano N**, Iijima K, Terai S, Jin X, Ara N, Chiba T, Fushiya J, Koike T, Imatani A, Shimosegawa T. Eradication therapy is effective for Helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma. *Tohoku J Exp Med* 2012; **228**: 223-227 [PMID: 23076291 DOI: 10.1620/tjem.228.223. Correspondence]

112 **Miyazaki T**, Ishiguro T, Ishibashi K, Itoyama S, Ishida H. Mucosa-associated lymphoid tissue lymphoma of the appendix vermiformis. *Int Surg* 2010; **95**: 27-32 [PMID: 20480837]

113 **Gardini A**, Saragoni L, La Barba G, Garcea D. Simultane-

ous occurrence of primary diffuse large B-cell lymphoma and extranodal marginal zone (MALT) B-cell lymphoma in the gallbladder: a case report. *Pathologica* 2009; **101**: 230-234 [PMID: 20387709]
114 **Deinbeck K**, Geinitz H, Haller B, Fakhrian K. Radiotherapy in marginal zone lymphoma. *Radiat Oncol* 2013; **8**: 2 [PMID: 23281682 DOI: 10.1186/1748-717X-8-2]
115 **Hancock BW**, Qian W, Linch D, Delchier JC, Smith P, Jakupovic I, Burton C, Souhami R, Wotherspoon A, Copie-Bergman C, Capella C, Traulle C, Levy M, Cortelazzo S, Ferreri AJ, Ambrosetti A, Pinotti G, Martinelli G, Vitolo U, Cavalli F, Gisselbrecht C, Zucca E. Chlorambucil versus observation after anti-Helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. *Br J Haematol* 2009; **144**: 367-375 [PMID: 19036078 DOI: 10.1111/j.1365-2141.2008.07486.x]
116 **Morgner A**, Schmelz R, Thiede C, Stolte M, Miehlke S. Therapy of gastric mucosa associated lymphoid tissue lymphoma. *World J Gastroenterol* 2007; **13**: 3554-3566 [PMID: 17659705]
117 **Avilés A**, Nambo MJ, Neri N, Talavera A, Cleto S. Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach: results of a controlled clinical trial. *Med Oncol* 2005; **22**: 57-62 [PMID: 15750197 DOI: 10.1385/MO::22:1:057]
118 **Jäger G**, Neumeister P, Quehenberger F, Wöhrer S, Linkesch W, Raderer M. Prolonged clinical remission in patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type treated with cladribine: 6 year follow-up of a phase II trial. *Ann Oncol* 2006; **17**: 1722-1723 [PMID: 16766585 DOI: 10.1093/annonc/mdl126]
119 **Kahl BS**, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, Czuczman MS, Robinson KS, Joyce R, van der Jagt RH, Cheson BD. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. *Cancer* 2010; **116**: 106-114 [PMID: 19890959 DOI: 10.1002/cncr.24714]
120 **Ben Simon GJ**, Cheung N, McKelvie P, Fox R, McNab AA. Oral chlorambucil for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue of the orbit. *Ophthalmology* 2006; **113**: 1209-1213 [PMID: 16647129 DOI: 10.1016/j.ophtha.2006.01.057]
121 **Conconi A**, Martinelli G, Lopez-Guillermo A, Zinzani PL, Ferreri AJ, Rigacci L, Devizzi L, Vitolo U, Luminari S, Cavalli F, Zucca E. Clinical activity of bortezomib in relapsed/refractory MALT lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group (IELSG). *Ann Oncol* 2011; **22**: 689-695 [PMID: 20810546 DOI: 10.1093/annonc/mdq416]
122 **Tektonidou MG**. MALT lymphoma of the lacrimal gland in the context of systemic lupus erythematosus: complete remission after treatment with rituximab. *Lupus* 2010; **19**: 1243-1245 [PMID: 20501524 DOI: 10.1177/0961203310367659]
123 **Shetty RK**, Adams BH, Tun HW, Runyan BR, Menke DM, Broderick DF. Use of rituximab for periocular and intraocular mucosa-associated lymphoid tissue lymphoma. *Ocul Immunol Inflamm* 2010; **18**: 110-112 [PMID: 20370339 DOI: 10.3109/09273940903450313]
124 **Nakajima T**, Yasufuku K, Sekine Y, Yoshida S, Yoshino I. Mucosa-associated lymphoid tissue lymphoma of the left mainstem bronchus. *Ann Thorac Surg* 2011; **91**: 1281-1283 [PMID: 21440165 DOI: 10.1016/j.athoracsur.2010.10.009]
125 **Kagawa M**, Okamura S, Okamoto K, Kitamura S, Kimura T, Niki M, Kaji M, Okahisa T, Yano M, Kagawa S, Kudo E, Sano T, Imoto Y, Wada S, Takayama T. Successful rituximab monotherapy in a patient with mucosa-associated lymphoid tissue lymphoma of the rectum with trisomy 3, 18. *Nihon Shokakibyo Gakkai Zasshi* 2010; **107**: 612-619 [PMID: 20379095]
126 **Kang HJ**, Kim WS, Kim SJ, Lee JJ, Yang DH, Kim JS, Lee SR, Lee GW, Kim HJ, Kim HY, Oh SY, Kim HC, Eom HS, Chung J, Park J, Suh C, Ryoo BY. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: Consortium for Improving Survival of Lymphoma (CISL) study. *Ann Hematol* 2012; **91**: 543-551 [PMID: 21922208 DOI: 10.1007/s00277-011-1337-6]
127 **Salar A**, Domingo-Domenech E, Estany C, Canales MA, Gallardo F, Servitje O, Fraile G, Montalbán C. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. *Cancer* 2009; **115**: 5210-5217 [PMID: 19672998 DOI: 10.1002/cncr.24605]
128 **Zucca E**, Conconi A, Laszlo D, López-Guillermo A, Bouabdallah R, Coiffier B, Sebban C, Jardin F, Vitolo U, Morschhauser F, Pileri SA, Copie-Bergman C, Campo E, Jack A, Floriani I, Johnson P, Martelli M, Cavalli F, Martinelli G, Thieblemont C. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. *J Clin Oncol* 2013; **31**: 565-572 [PMID: 23295789 DOI: 10.1200/JCO.2011.40.6272]
129 **Oh SY**, Kim WS, Kim JS, Kim SJ, Lee S, Lee DH, Won JH, Hwang IG, Kim MK, Lee SI, Chae YS, Yang DH, Kang HJ, Choi CW, Park J, Kim HJ, Kwon JH, Lee HS, Lee GW, Eom HS, Kwak JY, Suh C, Kim HJ. Stage IV marginal zone B-cell lymphoma--prognostic factors and the role of rituximab: Consortium for Improving Survival of Lymphoma (CISL) study. *Cancer Sci* 2010; **101**: 2443-2447 [PMID: 20831770 DOI: 10.1111/j.1349-7006.2010.01698.x]
130 **Hoffmann M**, Troch M, Eidherr H, Traub-Weidinger T, Jonak C, Muellauer L, Raderer M. 90Y-ibritumomab tiuxetan (Zevalin) in heavily pretreated patients with mucosa associated lymphoid tissue lymphoma. *Leuk Lymphoma* 2011; **52**: 42-45 [PMID: 21133720 DOI: 10.3109/10428194.2010.534519]
131 **Esmaeli B**, McLaughlin P, Pro B, Samaniego F, Gayed I, Hagemeister F, Romaguera J, Cabanillas F, Neelapu SS, Banay R, Fayad L, Wayne Saville M, Kwak LW. Prospective trial of targeted radioimmunotherapy with Y-90 ibritumomab tiuxetan (Zevalin) for front-line treatment of early-stage extranodal indolent ocular adnexal lymphoma. *Ann Oncol* 2009; **20**: 709-714 [PMID: 19150940 DOI: 10.1093/annonc/mdn692]

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