INDOLENT B-CELL LYMPHOMA

The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance

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Extranodal marginal zone (MZ) B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT) arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. The best evidence of an etiopathogenetic link is provided by the association between *Helicobacter pylori*–positive gastritis and gastric MALT lymphoma. Indeed, successful eradication of this microorganism with antibiotics can be followed by gastric MALT lymphoma regression in most cases. Other microbial agents have been implicated in the pathogenesis of MZ lymphoma arising at different sites. Apart from gastric MALT lymphoma, antibiotic therapies have been adequately tested only in ocular adnexal MALT lymphomas where upfront doxycycline may be a reasonable and effective initial treatment of patients with *Chlamydophila psittaci*–positive lymphoma before considering more aggressive strategies. In all other instances, antibiotic treatment of nongastric lymphomas remains investigational. Indeed, there is no clear consensus for the treatment of patients with gastric MALT lymphoma requiring further treatment beyond *H pylori* eradication or with extensive disease. Both radiotherapy and systemic treatments with chemotherapy and anti-CD20 antibodies are efficacious and thus the experience of individual centers and each patient's preferences in terms of adverse effects are important parameters in the decision process. (*Blood*. 2016;127(17):2082-2092)

The peculiar biology of MALT lymphomas

Marginal zone (MZ) lymphomas (MZLs) represent a group of lymphomas originating from B lymphocytes of the "marginal zone," which is the external part of the secondary lymphoid follicles. This anatomic compartment is more prominent in lymphoid organs that are continuously exposed to not only a high flow of external antigens, particularly the spleen, but also the mucosa-associated lymphoid tissue (MALT) and the mesenteric lymph nodes. The B cells resident in the MZ function as innate-like lymphocytes that mount rapid antibody responses to both T-cell–dependent and –independent antigens.[1] Most of the MZ lymphocytes are B cells that are involved in the T-cell–independent early immune response and express a restricted immunoglobulin repertoire. Post-germinal center memory B cells, needed for the T-cell–dependent immune response, are also localized in the MZ, as well as a variety of other immune system cells (plasma cells, dendritic cells, macrophages, T cells, and granulocytes) that interact with circulating antigens.

In the World Health Organization (WHO) classification, there are 3 different MZL entities with specific diagnostic criteria, different behavior, and therapeutic implications: the extranodal MZL of MALT type (MALT lymphoma), the splenic MZL, with or without villous lymphocytes, and nodal MZL.[2] The genetic relationship between the 3 MZL subtypes (nodal, extranodal, and splenic) is still unclear. A comprehensive analysis of DNA copy-number changes in a very large series of 218 MZL patients showed that the 3 MZL types share recurrent trisomies of chromosomes 3 and 18 and deletions at 6q23 (*TNFAIP3*).[3] MALT lymphoma presents more frequently gains at 3p, 6p, 18p, and the del(6q23).[3] Different from the other 2 MZL types, MALT lymphoma presents recurrent chromosomal translocations[4-11] (Table 1), and at least 3 of them lead to the activation of the nuclear factor κB (NF-κB) pathway,[23,24] which can also be constitutively turned on due to the inactivation of TNFAIP3 by either somatic mutation and/or del(6q23)[3,25,26] or, possibly, by stimulation of the Toll-like receptor signaling as suggested in splenic MZLs.[27] Nodal and splenic MZLs share recurrent mutations affecting the Notch pathway and the transcription factor KLF2, but differ for the inactivation of 2 tumor-suppressor genes, detected exclusively (*PTPRD*) or much more commonly (*KMT2D/MLL2*) in the nodal type.[28,29]

MALT lymphoma is the commonest MZL type, accounting for 5% to 8% of all B-cell lymphomas,[30,31] and has been described in virtually all tissues, often in organs that are normally devoid of germinal centers. Indeed, they arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. The most frequently affected organ is the stomach, where MALT lymphoma has been incontrovertibly associated with the chronic gastritis induced by *Helicobacter pylori* whereas a possible etiologic link has been shown between other microorganisms and MALT lymphomas arising in other anatomical sites.[32] In addition to infections, chronic inflammation caused by autoimmune diseases, such as Sjögren syndrome or Hashimoto thyroiditis, can also carry a significant risk for the development of MALT lymphoma.

Besides the continuous antigenic stimulation, additional oncogenic events play a relevant role in lymphoma growth and progression to the point where the lymphoproliferative process becomes frankly malignant and, eventually, independent of the antigenic drive.[32] This makes the differential diagnosis between the preexisting chronic inflammation and the MALT lymphoma not always straightforward: clonal B-cell expansions can be detected in benign inflammatory tissues, particularly in the context of autoimmune reactions. Also, the

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Table 1. Most common genetic aberrations detected in MALT lymphomas

Genetic lesion[3-22]	Involved genes	Deregulated pathway	Prevalence, %	Anatomical sites	Clinical relevance
t(11;18)(q21;q21)	BIRC3-MALT1	NF-κB	15-40	Stomach, lung	Antibiotic resistance alkylating agents resistance?
t(14;18)(q32;q21)	IGHV-MALT1	NF-κB	20	Lung, salivary gland, skin, ocular adnexa	Antibiotic resistance?
t(1;14)(p22;q32)	IGHV-BCL10	NF-κB	<5	Stomach, lung	Antibiotic resistance
t(3;14)(p13;q32)	IGHV-FOXP1	Wnt*	<5	Unclear	Transformation risk?
t(9;14)(p24;q32)	*IGHV-JMJD2C*	Chromatin remodeling†	<5	Unclear	
t(X;14)(p11;q32)	*IGHV-GPR34*	NF-κB ?	<5	Unclear	
t(5;14)(q34;q32)	*IGHV- TENM2*	Unclear	<5	Unclear	
Trisomy 3	Unclear	Unclear	20-40	Equal distribution	Inferior outcome?
Trisomy 18	Unclear	Unclear	20-40	Equal distribution	
del(6q23)	*TNFAIP3*	NF-κB	15-30	Equal distribution	

*DLBCLs bearing the same chromosomal translocation show deregulated Wnt signaling.[21]

†*JMJD2C* is amplified and overexpressed in other lymphoma subtypes in which its genetic silencing leads to decreased levels of H3K9me3, a marker of transcriptional repression.[22]

presence of the typical lymphoepithelial lesions is neither essential nor pathognomonic for the diagnosis of MALT lymphoma, as they can be detected in some reactive conditions or in other lymphoma subtypes.[33] Hence, having the diagnosis confirmed by an expert hematopathologist to avoid overtreatment of benign conditions is recommended.[33]

Diverse pathogenetic mechanisms may lead to diverse clinical outcomes not only from organ to organ[31] but also within the same organ[34]; these differences, particularly with respect to personalized medicine, might impact therapeutic approaches. This review will summarize the many faces of MALT lymphoma pathogenesis and the current evidence for site-directed treatments.

Antigen drive and genetic lesions

MZ B cells are continuously exposed to exogenous antigens and have a physiologically reduced threshold for triggering proliferation, which may predispose them to malignant transformation.[1]

As stated in the previous section, extranodal MZL most frequently occur in organs normally devoid of germinal centers following a process of chronic inflammation and antigenic stimulation, where genes that regulate apoptosis, cell survival, and proliferation play a prominent role. Autoimmune disorders are, in this context, considered a potential risk factor for the development of lymphomas. Indeed, patients with Sjögren syndrome have an extremely increased risk of developing a MZL.[35-38] The mechanisms might be, however, distinct in each autoimmune disease. In the case of the Sjögren syndrome, it has been hypothesized that a local chronic antigen drive activates the development of organized lymphoid tissue in lacrimal and salivary glands and that CD40/CD40 ligand (CD40L) and BCL2 family proteins together with the overexpression of B-cell–activating factor (BAFF) may lead to excessive autoantibody production and reduced apoptosis, providing a stimulus for sustained proliferation of B cells.[37,39,40] Individual genetic differences, highlighted by the recent report of polymorphisms near the *BTNL2* and *HLA-B* genes in the HLA region,[41] influence the susceptibility to develop MZL.

MALT lymphoma presents somatically mutated immunoglobulin heavy chain variable region (IGHV) genes in nearly all cases. IGHV sequence analysis shows a pattern of somatic hypermutation and rearrangement, suggesting that tumor cells have undergone antigen selection in germinal centers.[42] The presence of the so-called ongoing mutations (intraclonal variation) and the biased usage of some IGHV segments indicate that the expansion of lymphoma cells could still be antigen-driven. Interestingly, a specific usage of different restricted IGHV families appears associated with different anatomical sites or with particular clinical and genetic features: IGHVH1-69 in salivary gland lymphomas; IGHVH3-30 or IGHVH3-23 in gastric MALT lymphomas responsive to *H pylori* eradication and without the t(11;18) translocation; IGHVH4-34 in orbital adnexal lymphomas; IGHV3 and IGHV4 families in pulmonary lymphomas; and IGHVH1-69 or IGHVH4-59 in cutaneous lymphomas.[43] Also, the antibodies expressed by MALT lymphoma cells can present, although not always, specificity for self-antigens.[44-46]

As a clinicopathological entity, MALT lymphomas from different anatomical sites share common histological, clinical, and genetic features, but differences do exist.[47] The autoimmune or infective disorders that precede the lymphoma differ from site to site, and this can impact the clinical features, and, possibly, the genetic identity of the lymphoma. Indeed, the recurrent chromosomal aberrations occur at frequencies that vary according to anatomical localization.[9,12,48]

Main clinical characteristics of MALT lymphoma

The stomach is the commonest localization; frequent nongastric sites are: salivary glands, skin, orbits and conjunctiva, lung, thyroid, upper airways, breast, other gastrointestinal (GI) sites, and liver.[47,49-51] The anatomic site may have prognostic relevance because of organ-specific clinical problems but, because different genetic lesions may be associated with different localizations,[12] it is possible that the different sites have a distinct natural history. In a study evaluating the long-term outcome of 167 patients with localized (stage IE and IIE) MALT lymphoma treated with involved field radiotherapy, gastric and thyroid lymphomas had a significantly better outcome and distant failures were more common for other sites.[52] In general, despite frequent relapses, MALT lymphomas most often maintain an indolent course.[47] In the above-mentioned study, the 10-year recurrence-free rate was 76%, the overall survival rate was 87%, and the cause-specific survival rate was 98%.[52] Similar results were reported in a survey of 490 patients with stage I-II MALT lymphoma treated with radiotherapy only; the 10-year overall and recurrence-free survival were 79% and 57%, respectively, and patients with stomach or head and neck lymphomas had longer relapse-free survival.[53]

Within the same organ, the outcome may be different, possibly as a result of different pathogenetic pathways as suggested by the finding that, in gastric MALT lymphoma, the presence of MALT1 translocation confers resistance to antibiotic treatment or that, among the

Table 2. Recommended site-specific workup in MALT lymphomas

MALT lymphoma site	Site-specific staging procedures
Stomach	Ear/nose/throat examination, EGD, endoscopic ultrasound to evaluate regional lymph nodes and gastric wall infiltration, search for *H pylori* (histochemistry, serology, breath test, fecal antigen), search for MALT1 translocation by FISH
Salivary glands	Ear/nose/throat examination and ultrasound. Anti-SSA or anti-SSB antibodies for possible association with Sjögren syndrome
Thyroid	Ultrasound ± CT scan of the neck and thyroid function tests
Lung	Bronchoscopy with bronchoalveolar lavage
Small intestine	Search for *C jejuni* in the tumor biopsy (PCR, immunohistochemistry or in situ hybridization)
Large intestine	Colonoscopy
Breast	Mammography and MRI
Ocular adnexa	MRI and ophthalmologic examination. Search for *C psittaci* in the tumor biopsy and blood mononuclear cells by PCR may be considered
Skin	Search for *B burgdorferi* in the tumor biopsy by PCR may be considered in areas where it is endemic

EGD, esophagogastroduodenoscopy; FISH, fluorescence in situ hybridization; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SSA, Sjögren syndrome A; SSB, Sjögren syndrome B.

patients with salivary gland lymphomas, those with a history of Sjögren syndrome have a better survival compared with those without.[34] Because lymphomagenesis in these patients is related to chronic immune stimulation and dysregulation, these outcome differences may be reflective of the differing biology of MALT development. The prognostic impact of concomitant autoimmune disease remains, however, not yet fully elucidated. In a series of 158 MALT lymphoma patients, those with autoimmune disease were predominantly women and significantly younger at lymphoma diagnosis (56 vs 67 years), with a significantly higher rate of extragastric lymphomas.[54] The clinical course, however, did not appear to be adversely influenced by the presence of autoimmune diseases; apart from a lower response rate to *H pylori* eradication in patients with gastric lymphoma, neither times to relapse or survival significantly differed.[54]

Although up to one-third of diffuse large B-cell lymphoma (DLBCL) arise from extranodal sites, histological transformation of MALT lymphoma to large-cell lymphoma is comparatively less frequent than for follicular lymphomas with an occurrence well below 10% in most series, also occurring as a late event, independent from dissemination.[13,51,52,55-57]

MALT lymphoma characteristically remains localized for a prolonged period within the tissue of origin, but involvement of regional lymph nodes and spreading to multiple sites may occur. Localized MALT lymphoma is often multifocal within the involved organ (ie, stomach, skin), although this may not reflect a truly disseminated disease. The latter is reported in up to one-quarter of cases and is more common in non-GI MALT lymphomas.[47,50,51,55] Bone marrow infiltration is observed at a similar frequency, occurring in up to 20% of cases.[58] Patients with lymph node or bone marrow involvement at presentation, but not those with involvement of multiple mucosal sites, are associated with a worse prognosis.[47]

Due to the risk of occult-disseminated disease, extensive initial staging assessment is indicated regardless of the presentation site,[59] particularly if antibiotic treatment or localized radiotherapy is planned. Besides standard computerized tomography (CT) scan imaging of the chest and abdomen, recommended site-specific procedures are reported in Table 2.[33,59] The value of the positron emission tomography (PET) scan is still unclear. In general, the use of PET-CT scan in the routine staging of MZL is not recommended,[33,59] except for selected cases (ie, when a transformation to high-grade lymphoma is suspected). However, there is some growing evidence that many nongastric sites are usually PET-positive.[60,61] In a meta-analysis of the published literature up to 2014,[60] the pooled detection rate of ^{18}fluorodeoxyglucose (F-FDG) PET or PET-CT in MALT lymphomas was 71%, and appeared particularly high in the pulmonary (94%) and head and neck (90%) localizations, showing that MALT lymphoma can often be FDG-avid and suggesting a potentially relevant role of PET-CT in the initial evaluation of these patients, especially when the disease is apparently localized and radiotherapy is planned.

Association of different infectious agents with MALT lymphomas at various anatomical sites: therapeutic implications

Several lines of epidemiologic, biologic, and clinical evidence indicate that gastric MALT lymphoma arises from MALT acquired as a consequence of chronic *H pylori* infection. Outside of the stomach, the acquisition of MALT can be induced by a series of agents, which are different for each anatomic site. Other bacterial infections have been implicated in the pathogenesis of MZL arising in the skin (*Borrelia burgdorferi*),[62] in the ocular adnexa (*Chlamydophila psittaci*),[63] in the small intestine (*Campylobacter jejuni*),[64] and possibly in the lung (*Achromobacter xylosoxidans*).[65] An increased risk has been reported in patients with chronic hepatitis C virus (HCV) infection to develop not only splenic and nodal MZLs but also MALT lymphomas.[36,66,67] The association with HCV, however, shows considerable and not entirely explained geographic discrepancies.[68] These site-specific biological differences might influence outcome, and recognition of the driving source of the antigenic stimulation in different tissues may have important therapeutic implications. Although antibiotic therapy is nowadays well established for primary gastric MALT lymphoma, much less is known about the value of anti-infectious therapy in other MALT lymphomas (Table 3[69-72]).

Helicobacter pylori and the gastric MALT lymphoma pathogenetic model

Initially, *H pylori* was demonstrated in the gastric mucosa of over 90% of gastric MALT lymphoma cases,[73] but there are both geographical[74] and temporal variations.[75] In particular, a population-based study from Northern Italy showed a declining incidence of *H pylori*–associated gastric MALT lymphomas in the last decade, most likely due not only to a decreasing prevalence of the infection but also to the now common policy of an early generalized use of proton pump inhibitors (PPIs) without a diagnostic gastroscopy in patients with acid peptic disease symptoms.[75]

Direct evidence confirming the importance of *H pylori* in the pathogenesis of gastric lymphoma derives from studies detecting the lymphoma B-cell clone in the chronic gastritis that preceded the lymphoma[67,76] and from a series of preclinical studies showing that

Table 3. Antibiotic-induced lymphoma remission in MALT lymphomas

Involved organ	Targeted pathogen	Antibiotic regimen	No. of patients	Type of study	Overall lymphoma remission rate, %
Stomach	*H pylori*	Mostly PPI plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10-14 d	1408	32 studies either retrospective or prospective	77.5
Ocular adnexa	*C psittaci*	Doxycycline 100 mg Twice daily ×21 d	120	2 prospective, 4 retrospective, 1 case report	48
		Clarithromycin* 500 mg Twice daily ×6 mo	11	Prospective	45
		Clarithromycin* 2 g/d, days 1-14, every 21 d (4 courses)	23	Prospective	52
Skin	*B burgdorferi*	Ceftriaxone 2 g/d ×14 d (in most cases)	5	Case reports	40

*The clarithromycin activity may also depend on the immunomodulatory and direct antitumor effect of this macrolide antibiotic.[71]

H pylori can contribute to MALT lymphoma pathogenesis both directly, acting on the still normal and then transformed B cells, and indirectly, affecting other immune cells such as T cells.[32,77] A main role is played by the *H pylori* cytotoxin-associated gene A (CagA) protein, also involved in gastric cancer pathogenesis.[78,79] Interindividual differences in antioxidative capacity and in the cellular inflammatory responses to *H pylori* may represent the genetic background of the *H pylori*–associated gastric lymphomagenesis.[80,81]

All of the above-summarized findings are in keeping with a possible model of multistage development and progression from chronic gastritis to gastric lymphoma that starts with chronic *H pylori* infection, stimulating the formation of a lymphocytic infiltration in the gastric mucosa. As a result of an antigenic stimulation (autoantigens and T cells specific for *H pylori*) combined with a direct effect on B cells, the latter proliferate and may occasionally undergo neoplastic transformation following the acquisition of genetic abnormalities, perhaps facilitated by the presence of free radicals.[10,80] The accumulation of genetic abnormalities would be associated with both a loss of dependency from antigenic stimulation (with subsequent antibiotic resistance) as well as a possible histological transformation. Notably, although additional evidence derived from large prospective studies is needed before routinely adopting such an approach, pathological lymphoma remissions after first-line *H pylori* eradication therapy have also been reported in some patients with *H pylori*–positive early-stage DLBCL of the stomach with or without concomitant or prior histological evidence of MALT lymphoma.[82-84] This finding suggests that the loss of antigen dependence and high-grade transformation may be separate events in the progression of gastric lymphoma. Of clinical relevance, although MALT lymphomas bearing the t(11;18) present a lower risk of transformation to DLBCL, the t(11;18)-positive primary gastric MALT lymphomas have a low probability of response to antibiotics and are more commonly *H pylori* negative, with more advanced disease.[14,85,86] Also, the t(3;14) has been associated with a risk of transformation to high-grade tumors.[13,15]

Antibiotic treatment of *Helicobacter pylori*–positive gastric MALT lymphoma

Eradication of *H pylori* with antibiotics should be the sole initial therapy for a localized *H pylori*–positive gastric MALT lymphoma (Figure 1). It results in lymphoma regression and long-term clinical control in most patients.[69,87] Several effective anti-*H pylori* treatments are available. The choice should be based on the epidemiology of the infection and on the expected antibiotic resistance in different countries. The most commonly used regimen comprises a PPI associated with clarithromycin and amoxicillin, administered for 10 to 14 days. Metronidazole can be used instead of amoxicillin for penicillin-allergic patients. *H pylori* eradication with antibiotics leads to gastric MALT lymphoma regression in 75% of cases.[69]

Detailed guidelines for response assessment and follow-up have been recently published[33] and our current algorithm for the management of stage IE-IIE gastric MALT lymphoma is summarized in Figure 1. It is important to recall that transient histological relapses can be observed in endoscopic biopsies during long-term follow-up, but they tend to be self-limiting, and importantly without the stimulus from *H pylori* reinfection, they do not implicate a true clinical relapse. Hence, when persistent but not progressive residual disease or histological relapse is documented, a "wait-and-see" policy seems safe.[87-90] Nevertheless, a long-term careful endoscopic and systemic follow-up (clinical examination, blood counts, and minimal adequate radiological or ultrasound examinations every 12-18 months) is strongly advisable for all patients. Indeed, the risk of gastric adenocarcinoma among individual with gastric MALT lymphoma can be up to sixfold higher, and the risk of other lymphomas is higher than in the general population.[91,92]

Antibiotic treatment of *Helicobacter pylori*–negative gastric MALT lymphoma

There are also reports of lymphoma regression following antibiotics in *H pylori*–negative patients, possibly due to a false-negative test or to infection by other *Helicobacter* species.[93] Hence, first-line therapy with antibiotics may be considered at least in those patients without the t(11;18) translocation. However, an oncological treatment is to be considered when no signs of lymphoma regression are seen at a repeated endoscopy assessment 2 to 3 months after antibiotics administration.

Chlamydophila psittaci and ocular adnexal MZL

Besides *H pylori*, *C psittaci* is the most thoroughly studied among the other bacteria reported to have a potential pathogenetic role in MZL. *Chlamydophila* is the etiologic agent of psittacosis, an infection caused by exposure to infected animals. The presence of *C psittaci* DNA has been detected not only in a variable percentage of MZL, mainly of the ocular adnexae (ie, conjunctiva, lachrymal gland, orbital fat, eyelid, lachrymal sac), but also in MZL of the lungs, skin, thyroid gland, and salivary glands. However, it should be noted that the prevalence of *C psittaci* infection in ocular adnexal marginal zone lymphoma (OAMZL)

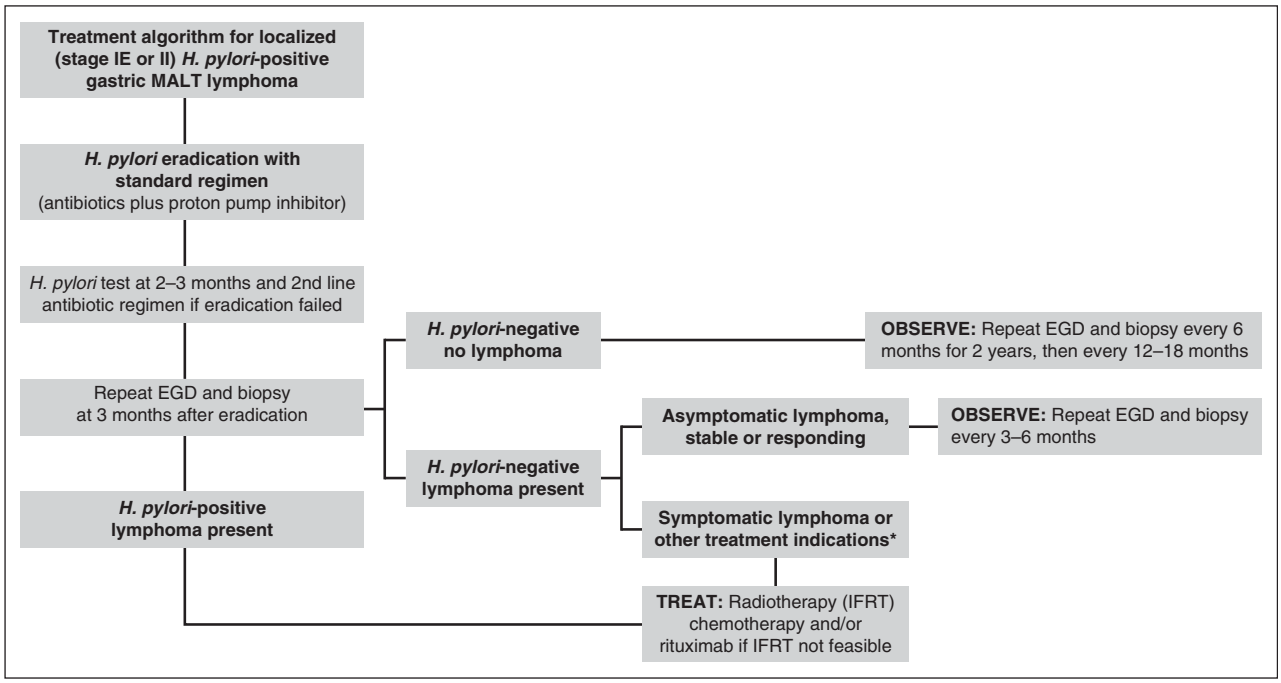

Figure 1. Treatment algorithm for the management of gastric MALT lymphoma confined to the stomach, with or without regional lymph node involvement. It is currently recommended that gastric biopsies are evaluated using the Group d'Etude des Lymphomes de l'Adult (GELA) scoring system.[33] *Indications to treat comprise overt progression, deep gastric wall invasion, regional lymph node involvement, t(11;18) translocation. EGD, esophagogastroduodenoscopy; RT, involved-field radiotherapy (24-30 Gy to the stomach and perigastric nodes given in 3-4 weeks).

varies among countries and different regions within the same country, being higher in Italy, Austria, Korea, and Germany (with prevalence rates up to 80%), and virtually absent in Japan, France, and China.[32]

Evidence supporting a pathogenic association between *C psittaci* and the development of MALT lymphoma of the ocular adnexa comprises the identification of *Chlamydophilae* in tumor tissue by immunohistochemistry and the detection of bacterial DNA in the tumor biopsies, bacterial visualization within tumor-infiltrating macrophages by electronic microscopy, their isolation from conjunctival swabs and from the ocular adnexa peripheral blood of patients,[94,95] as well as the description of metachronous *C psittaci*–related lymphomas observed in the same patient after prolonged exposure to an infected animal.[96]

Globally, doxycycline has been tested in >100 patients with OAMZL (Table 3), showing an overall response rate (ORR) of around 50%.[70] The median time for response after antibiotic therapy is 6 months but in some patients responses are slow and may require up to 36 months.[97] In a prospective phase 2 study, *C psittaci* DNA was detected in nearly 90% of lymphoma biopsy specimens.[94] Front-line doxycycline induced *Chlamydophila* eradication in 14 of 34 patients (48%); 6 patients obtained complete lymphoma regression (ORR, 65%).[94] At a median follow-up of 37 months, the 5-year progression-free survival was 55%.[94] However, lymphoma regression after doxycycline treatment has been observed in some lymphomas with no *C psittaci* presence as well as in cases where this treatment failed to eradicate the *C psittaci* infection,[94,97,98] suggesting that other doxycycline-sensitive microorganisms might be involved.[99]

In a small exploratory study, lymphoma regressions were seen after a 6-month oral clarithromycin regimen in 5 of 11 patients with ocular adnexal MALT lymphoma[71] who had been previously unsuccessfully treated with doxycycline. A subsequent phase 2 trial tested the activity of a higher clarithromycin dose in 23 MALT lymphoma patients with relapsed/refractory disease. Ocular adnexae were the most commonly involved organs. Six patients achieved a complete remission (CR) and 6 a partial response (ORR, 52%; 95% confidence interval, 32%-72%). At a median follow-up of 24 months, only 2 patients with responsive disease experienced relapse.[72]

Borrelia burgdorferi in cutaneous MZL

The prevalence of *B burgdorferi* infection in patients with cutaneous MZL exhibits important variations among different geographic areas, with higher detection rates in areas where it is endemic. In Europe, DNA of *B burgdorferi* has been detected in 10% to 42% of patients.[99] Anecdotal case reports have shown that the eradication of *B burgdorferi* following ceftriaxone therapy resulted in regression of an associated cutaneous MZL[62,70] (Table 3), corroborating the hypothesis that chronic *B burgdorferi* infection could represent the background for the development of cutaneous MZL.[32]

The demonstration of a *B burgdorferi* infection may be sought in areas of endemicity, where it may have some therapeutic implications; however, the evidence is based on a limited number of patients and therefore no recommendations can be made.

Immunoproliferative small intestinal disease and *Campylobacter jejuni*

Endemic in the Middle East, the immunoproliferative small intestinal disease (IPSID), previously also known as α-heavy-chain disease or

Mediterranean lymphoma, is a special subtype of MALT lymphoma. Sporadic cases can also be diagnosed in Western countries, often among immigrants from the area of endemicity.[100,101]

IPSID has a long natural history, often over many years, including a potentially reversible early phase. If left untreated, however, the lymphoma can transform to DLBCL.

The restricted geographic distribution of IPSID supports the hypothesis that environmental factors may have a relevant pathogenetic role. It has been known since the 1970s that in its early phases, IPSID can be treated with antibiotic treatment (such as tetracycline or metronidazole and ampicillin for at least 6 months), which can lead to durable remissions in the majority of patients. These results suggest a role for an infectious agent, and *Campylobacter jejuni* is so far the best, although not necessarily the sole, candidate.[64] Indeed, the level of evidence supporting a pathogenetic link of *C jejuni* with IPSID remains weak, with lymphoma improvement in 2 patients treated with antibiotics against *C jejuni*[99] and a unique study, describing the presence of *C jejuni* DNA in 5 of 7 archival cases followed by a single confirmatory case report.[64]

Achromobacter xylosoxidans and pulmonary MALT lymphoma

A xylosoxidans is a gram-negative bacterium characterized by a low virulence but high resistance to antibiotic therapy. It has been recurrently isolated from patients affected by cystic fibrosis and, in these patients, it is correlated with more severe lung damage. A study of 124 pulmonary MALT lymphoma biopsies and 82 nonlymphoma lung biopsies from 6 European countries showed a significantly increased prevalence of *A xylosoxidans* infection in MALT lymphomas than in control tissues[65] Overall, 46% of pulmonary MALT lymphomas and 18% of controls were positive although the infection prevalence among lymphoma patients varied among countries (ranging from 67% in Italy, to 33% in the United Kingdom).[65] Further studies are warranted to investigate the potential pathogenetic role of the microorganism because no data demonstrating a causal relationship has yet been provided[102] and other microorganisms (*Chlamydophila*) were reported as possibly involved with MALT lymphoma of the lung.[103] Moreover, a previous history of lymphocytic interstitial pneumonia, which is frequently associated with autoimmune disorders, or of other rare nonneoplastic pulmonary lymphoid proliferations (follicular bronchiolitis and nodular lymphoid hyperplasia) support the concept that lymphoma may also evolve from these noninfectious inflammatory processes.[104]

Other bacterial infections at different MALT sites

Several case reports and small series have described the potential association of various chronic infections with MALT lymphomas localized in the lungs, parotid and salivary glands, breast, thyroid, and bladder but some of these studies showed controversial results.[70,99,103] No conclusion can be drawn from the available information on antibiotic treatment in these lymphomas; the published data are scanty and possibly biased by the preferential publication of positive results.[70,99]

HCV and MALT lymphomas

Numerous epidemiological, clinical, and biological data have suggested an association between HCV infection and the pathogenesis of at least a portion of B-cell lymphomas, including MALT lymphomas, although with important geographical variations. Importantly, the strongest evidence for a causal relationship between HCV and lymphoma comes again from the observation of lymphoma regression after antiviral treatment.[68,105,106] Several potential pathogenic mechanisms have been advanced to explain a causative link with lymphoma growth[68,107]: a nondirect antigen-driven stimulation; a direct oncogenic role of HCV; a viral immunosuppressive effect on the tumor cells; and the co-infection by another unknown oncogenic virus.

MALT lymphomas in HCV-infected patients are most common at nongastric sites, often the salivary or lacrimal glands.[66,108-110] A rare clinical presentation has been described, namely the subcutaneous "lipoma-like" MALT lymphoma. This condition typically affects elderly women and exhibits single or multiple soft and mobile subcutaneous nodules that may regress after HCV eradication.[111]

Treatment of MALT lymphoma patients with advanced-stage disease or failing antibiotic therapies

There is no clear consensus for the treatment of patients with gastric MALT lymphoma requiring further treatment beyond *H pylori* eradication or with extensive disease.[47,50,51,55]

No significant survival difference between patients who received different initial treatments (including chemotherapy alone, surgery alone, surgery with additional chemotherapy, and radiation therapy) has been shown.[112,113] However, patients with extragastric lymphoma treated with antibiotics alone may have inferior remission rates and time to next therapy.[114] Radiotherapy may be the favored choice for patients with *H pylori*–negative localized disease or for patients who do not achieve a lymphoma regression following antibiotic therapy.[53] Indeed, involved-field radiotherapy to the stomach and perigastric lymph nodes has been shown to allow for excellent disease control, and most reports support the use of a moderate-dose (24-30 Gy given during a period of 3-4 weeks).[52,115-117] Literature reports a high rate of local control also in nongastric localizations, in which this therapeutic modality has been recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.[118] Modern radiotherapy techniques, such as 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy, allow an accurate determination of the clinical target volume, thus reducing toxicity to surrounding organs.[116] The moderate radiation doses required for cure (25-35 Gy) are generally associated with mild and reversible acute toxicity and a low risk of long-term side effects, although special caution should be given for specific localizations such as the ocular adnexa or the lung.[52,116]

In the case of patients with disseminated nongastric MALT lymphoma, observation with careful monitoring can often prove an adequate initial approach. When treatment is required, there is no consensus for the choice of treatment, but rituximab plus chemotherapy appears the most appropriate choice. The treatment approach of disseminated MALT lymphomas is the same in patients with primary gastric and nongastric origin and enrollment in controlled clinical trials is advisable. Indeed, there are no standard recommendations, as only a

Table 4. Targeted agents in patients with MALT lymphoma: single agents and combinations

Agents	Study type	No. of cases	ORR, %	CR, %
Single-agent trials				
Abexinostat[126]	Phase 2	13*	15*	0*
Bortezomib[127]	Phase 2	32	48	31
Entospletinib[128]	Phase 2	17*	18*	0*
Everolimus[129]	Phase 2	16	25	6
Ibrutinib[130]	Phase 1	4*	25*	0*
Idelalisib[131,132]	Phase 1	3*	0*	0
Idelalisib[131,132]	Phase 2	9*	56*	11
Lenalidomide[133]	Phase 2	18	61	33†
Tazemetostat[134]	Phase 1	1*	100*	n.a.
Thalidomide[135]	Phase 2	8	0‡	0‡
Combination trials				
Bortezomib, rituximab[136]	Phase 2	8*	50*	n.a.
Ibrutinib, lenalidomide[137]	Phase 1	2*	50*	0*
Ibrutinib, rituximab, bendamustine[138]	Phase 1	1*	100*	0*
Idelalisib, lenalidomide, rituximab[139]	Phase 1	1*	n.a.§	n.a.§
Lenalidomide, rituximab[140]	Phase 2	46	80	54
Lenalidomide, rituximab[141]	Phase 2	27*	89*	67*
Lenalidomide, rituximab, bendamustine[142]	Phase 1	3*	67*	0*
Venetoclax, bendamustine, rituximab[143]	Phase 1	4*	75*	25*

Data were collected from full papers and from abstracts presented at the 2015 meeting of the American Society of Hematology with results available for MZL patients.

n.a., not available.

*Unspecified whether MALT lymphoma, splenic MZL, or nodal MZL.

†39% CR at a later report.[144]

‡25% ORR, 25% CR at a later report.[144]

§Trial stopped after 7 lymphoma patients due to hepatotoxicity.

limited number of drugs and regimens have been specifically tested in MALT lymphomas.[119] Oral alkylating agents (either cyclophosphamide or chlorambucil) or purine nucleoside analogs (fludarabine, cladribine) are active as single agents.[58,119] Rituximab monotherapy has also been tested in phase 2 studies.[120,121] The efficacy and safety of the combination of rituximab plus chlorambucil has been proven in a phase 3 International Extranodal Lymphoma Study Group (IELSG) study in gastric (failing antibiotics) or nongastric MALT lymphomas. In comparison with either rituximab or chlorambucil given as single agent, chlorambucil plus rituximab resulted in significantly superior CR, progression-free and event-free survival rates; however, no overall survival benefit was shown.[122,123] The combination of rituximab and bendamustine[124] as well as the combination of fludarabine and rituximab have also shown high rates of disease control in smaller nonrandomized studies.[125] The significant hematological and infectious toxicity observed with the latter regimen, both during and after therapy, was deemed too high in this patient population.[125] As shown in Table 4,[126-144] new targeted agents have been poorly studied in MALT lymphomas: only 3 studies[127,129,133] were restricted to this entity and included >10 patients.

Aggressive anthracycline-containing chemotherapy regimens should be reserved for patients with high tumor burden (bulky masses, unfavorable International Prognostic Index) or for those with histological transformation.[145]

Antibiotic therapy in gastric diffuse large B-cell lymphoma

Although patients with gastric DLBCL can achieve tumor regression after anti-*Helicobacter* therapy,[82-84] additional evidence derived from large prospective studies is needed before routinely adopting this approach, and, at present, we recommend treating gastric large-cell lymphomas according to the guidelines for localized DLBCL.[146] Antibiotic therapy as first-line treatment of these patients is not advised outside of clinical trials until evidence is derived from large prospective studies.

Conclusions

No definite guidelines exist for the management of nongastric MALT lymphoma (nor for *H pylori*–negative cases). Apart from gastric MALT lymphoma, antibiotic therapies have been extensively tested only in ocular adnexal MALT lymphomas where, with negligible toxicity, the outcome of doxycycline therapy, although lacking long-term follow-up information, seems not inferior to the outcome reported for chemotherapy and radiotherapy, suggesting

Table 5. Phase 2 and 3 clinical trials recruiting patients with MALT lymphoma

Study type	Clinical trial registration no.	Trial arms	Patient population	Study sponsor
Phase 3	NCT00877214	Rituximab maintenance of 2 y vs 4 y	U	Academy
Phase 3	NCT01732913	Idelalisib vs idelalisib plus rituximab	R/R	Industry
Phase 3	NCT01938001	Rituximab/lenalidomide vs rituximab	R/R	Industry
Phase 3	NCT01974440	BR or R-CHOP vs BR plus ibrutinib or R-CHOP plus ibrutinib	R/R	Industry
Phase 3	NCT01996865	Lenalidomide/rituximab followed by lenalidomide vs lenalidomide/rituximab followed by rituximab	R/R	Industry
Phase 2	NCT00923663	Lenalidomide	R/R	Academy
Phase 2	NCT01514344	Intralesional rituximab	R/R	Academy
Phase 2	NCT01516606	Clarithromycin	R/R	Academy
Phase 2	NCT01678404	^{131}I-rituximab	R/R	Academy
Phase 2	NCT01808599	Chlorambucil and subcutaneous rituximab	U	Academy
Phase 2	NCT01820910	Doxycycline	U	Academy
Phase 2	NCT02086591	Doxycycline	R/R	Academy
Phase 2	NCT02332980	Pembrolizumab	R/R	Academy
Phase 2	NCT01995669	Lenalidomide plus obinutuzumab	R/R	Academy
Phase 2	NCT02433795	Bendamustine plus rituximab	R/R	Academy

Trials have been selected if registered at ClinicalTrials.gov, and marked as recruiting on December 12, 2015. Sorted by study type and clinical trial registration number.
BR, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristin, prednisone; R/R, relapsed/refractory; U, untreated.

that upfront doxycycline is a reasonable and effective treatment proposal for patients with stage I *C psittaci*–positive ocular adnexa MALT lymphoma before considering more aggressive strategies.[94] In all other instances, antibiotic treatment of nongastric lymphomas remains investigational. Radiotherapy can be effective in providing local disease control even for some patients with disseminated disease.[53] However, there is no clear consensus as to whether radiation is more or less effective than systemic therapy in MALT lymphomas at different locations, and the experience of each center and the patient's preferences in terms of adverse effects are important parameters in the decision process.[147] Because no curative treatment exists, expectant observation can be an adequate initial policy in most patients with disseminated disease. In general, the treatment should be ''patient-tailored,'' taking into account the site, the stage, and the clinical characteristics of the individual patient. When systemic treatment is needed, chemotherapy (and/or immunotherapy with anti-CD20 monoclonal antibodies) can be considered. In this context, enrollment in controlled clinical trials (Table 5) is advisable because only a few compounds and regimens have been specifically tested in the setting of MALT lymphomas.

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