



**Review Article**

## Infectious Aetiology of Marginal Zone Lymphoma and Role of Anti-Infective Therapy

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**Abstract.** Marginal zone lymphomas have been associated with several infectious agents covering both viral and bacterial pathogens and in some cases a clear aetiological role has been established. Pathogenetic mechanisms are currently not completely understood. However, the role of chronic stimulation of the host immune response with persistent lymphocyte activation represents the most convincing explanation for lymphoproliferation. Gastric MALT lymphoma is strictly associated with *Helicobacter pylori* infection and various eradicating protocols, developed due to increasing antibiotic resistance, represent the first line therapy for gastric MALT. The response rate to eradication is good with 80% of response at 1 year; this finding is also noteworthy because it recapitulates cancer cured only by the antibacterial approach and it satisfies the Koch postulates of causation, establishing a causative relationship between Hp and gastric MALT lymphoma. Patients with chronic HCV infection have 5 times higher risk to develop MZL, in particular, an association with splenic and nodal MZL has been shown in several studies. Moreover, there is evidence of lymphoma regression after antiviral therapy with interferon+ribavirin, thus raising hope that newly available drugs, extremely efficient against HCV replication, could improve outcome also in HCV-driven lymphomas. Another case-study are represented by those rare cases of MZL localized to orbital fat and eye conjunctivas that have been associated with *Chlamydochlamydia psittaci* infection carried by birds. Efficacy of antibacterial therapy against *C. psittaci* are conflicting and generally poorer than gastric MALT. Finally, some case reports will cover the relationship between primary cutaneous B-cell Lymphomas and *Borrelia Burgdorferi*.

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**Introduction.** Marginal zone lymphoma (MZL) is a heterogeneous group of low-grade, B-cell, non-Hodgkin lymphomas comprising three distinct diseases: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL), and nodal MZL (NMZL).<sup>1</sup> In recent European studies, MZL has been reported in 12% of new lymphoma diagnoses,<sup>2</sup> while a lower incidence of 3% was reported in the United States from Surveillance, Epidemiology, and End Results (SEER) registries.<sup>3</sup> Various contributing factors have been defined in terms of pathogenesis, including autoimmune diseases

(mainly Sjögren syndrome and chronic autoimmune thyroiditis)<sup>4</sup> while also several infectious agents are known or simply suspected to cause MZL. Mainly three mechanisms linking infections to MZL have been hypothesized:

1) lymphocyte-transforming viruses can infect lymphocytes inducing dysregulation of normal cell functions and promotion of cell division (Epstein-Barr virus, Human Herpesvirus 8, Human T-lymphotropic virus type I);

2) induction of immune suppression through progressive depletion of CD4+ T-lymphocytes, as in

AIDS (Human immunodeficiency virus) or in patients submitted to therapeutic immunosuppression;

3) stimulation of chronic immune response and persistent lymphocyte activation (*Helicobacter pylori*, Hepatitis C virus, *Chlamydomphila psittaci*, *Borrelia burgdorferi*, *Campylobacter jejuni*).<sup>5</sup>

Specific organisms have been implicated in the aetiology of MZL involving particular anatomic sites:<sup>6</sup> *Helicobacter pylori* for the stomach, *Chlamydomphila psittaci* for the ocular adnexa, *Borrelia burgdorferi* for the cutis, *Campylobacter jejune* for the small intestine, *Mycobacterium spp.* For the bronchus, Hepatitis C virus (HCV) for splenic and nodal MZL. However, a robust association is present only in gastric MALT lymphoma with *Helicobacter pylori* (*Hp*), where 90% of cases are Hp+.<sup>7</sup> Moreover, Hp eradication therapy is effective in gastric MALT Hp+ lymphoma with a remission rate around 80%<sup>8,9</sup> and also long-term results are excellent.<sup>10</sup> The studies on *Hp* and gastric MALT lymphoma have profoundly influenced our understanding of the pathogenesis of lymphomas and modified our management, because, for the first time in the history of medical oncology, cancer has been cured by antibiotic therapy.

This review focuses on the role of pathogens and development of MZL, with implication on the therapeutic option to target the implied infectious agents.

### Gastric MALT Lymphoma.

The clinical presentation of gastric involvement by MALT lymphoma is variable and not specific with abdominal pain being the most common symptom, followed by dyspepsia, vomiting, nausea and anorexia; weight loss is common; gastric bleeding occurs as presenting symptom in 20%–30% of patients, while gastric occlusion and perforation are less common.<sup>11</sup> Diagnosis is made after histopathological evaluation of gastric biopsy, generally after esophagogastroduodenoscopy, and rely on the morphologic demonstration of the “hallmark” of MALT lymphoma: the lymphoepithelial lesion that results from invasion by atypical lymphocytes of epithelial mucosa and invasion of the glandular epithelium, as well as reactive lymphoid follicles.<sup>12</sup> Paradoxically, the stomach is the commonest site of MALT lymphoma, despite MALT tissue is not normally present in gastric mucosa. However, differentiation from other indolent lymphomas (Follicular lymphoma, Mantle-cell lymphoma) and aggressive lymphoma (Diffuse large B-cell lymphoma and Peripheral T-cell lymphoma) is not always straightforward, and a minimum immunohistochemistry panel including CD20, CD10, CD5 and cyclin D1 is recommended.<sup>13</sup> Since the diagnosis should be made according to the WHO criteria,<sup>14</sup> it should be reviewed by an expert

hematopathologist.<sup>15</sup> Since the first discovery in 1982 by the Nobel prize-winning authors, B. Marshall and R. Warren<sup>16</sup> *Helicobacter pylori* has become critical for treating and studying gastric disease like peptic ulcer, MALT lymphoma and gastric cancer.<sup>17</sup> Hp identification mainly relies on histology (HE and modified Giemsa staining) and culture or invasive molecular tests.<sup>18</sup> In the case of negativity, serology should be performed to identify truly negative gastric MALT lymphomas,<sup>19</sup> in fact, Hp mucosal colonisation is not uniform, but in patches;<sup>20</sup> therefore, the infection can go undiagnosed if biopsy involves a non-colonised area. In addition, it is believed that extensive mucosal lesion secondary to lymphoma may reduce the density of the infection to even undetectable levels.<sup>21,22</sup>

**Role of *H. Pylori* in MALT Lymphoma.** *Helicobacter* species are the indigenous biota of mammalian stomachs, and *H. pylori* is the human-specific inhabitant,<sup>23</sup> there is evidence that *H. pylori* has been present in humans at least since ancestors of Amerindians migrated from Asia more than 11,000 years ago.<sup>24</sup> In this long time span, Hp has adapted to human gastric environment establishing an interaction that can be interpreted as both commensalism and long-term parasitism.<sup>25</sup> Extensive allelic diversity and genetic variability are hallmarks of this microaerophilic gram-negative bacterium,<sup>26</sup> resulting from the combination of a high mutation rate<sup>27</sup> and frequent exchange of genetic material during mixed strains infections.<sup>28</sup> That extraordinary capacity of adaptation to human host (resembling a quasispecies) is the key to the success for this microorganism to infect more than one-half of the human population. *H. pylori* has been established by *International Agency for Research on Cancer* (IARC) to be definitive bacterial carcinogen for humans<sup>29</sup> and is estimated to be responsible for 5.5% of all human cancer cases, about 592,000 new gastric cancer.<sup>30</sup> Spectrum of *H. pylori* infection is wide with most carriers remaining asymptomatic while patients with duodenal ulcer have antral predominant gastritis with little mucosal atrophy and hyperacidity; patients with gastric ulcer almost invariably have corpus predominant gastritis and hypoacidity with various degree of mucosal atrophy,<sup>31</sup> the latter condition is associated with gastric cancer.<sup>32</sup> Moreover, the case of gastric MALT lymphoma is a rarer condition, accounting for <5% of primary gastric neoplasms. The epidemiological data raise the question why some people develop gastric cancer (also MALT lymphoma), and others do not? For example, what is the possible answer to the ‘African enigma’ where ubiquitous *H. pylori* infections is not associated with gastric cancer but only gastritis?<sup>33</sup> On the other hand, in the setting of a developed Country like the Nord-East of Italy, where there is a higher prevalence of HP infection there is a concomitant high incidence of gastric lymphoma.<sup>34</sup>

Given that some simulations indicate that Hp seems to have spread from East Africa around 58,000 years ago following human migrations,<sup>35</sup> we could hypothesize that in Africa, where *H. pylori* have interacted for more time with its human host, it could have reached a better symbiotic state with a decreased virulence.

**Pathogenesis of *Helicobacter Pylori*-Induced Gastric MALT Lymphoma.** There are several known mechanisms that *Helicobacter* exploits to interact with the host mucosa. Actually, *H. pylori* strains can be broadly categorized into strains that express multiple factors that interact with host tissue (CagA, s1-VacA, BabA, OipA) and strains that lack these factors (36). In 1989, CagA was firstly identified<sup>37</sup> and is now recognized as a marker for strains that confers increased risk for peptic ulcer disease<sup>38</sup> and gastric cancer.<sup>39</sup> The Cag Type IV secretion system (T4SS) is the primary virulence determinant and is responsible for injecting macromolecules, in particular, CagA, inside epithelial cells.<sup>40</sup> CagA is then tyrosine-phosphorylated by the host cell Src kinase; once phosphorylated, CagA interacts with SHP-2, a tyrosine phosphatase, which affects spreading, migration, and adhesion of epithelial cells.<sup>41</sup> Moreover, CagA protein interacts with Grb2 and activates the Ras/MEK/ERK pathway, leading to the phenotypes of cell scattering and proliferation.<sup>42</sup> In addition, tyrosine-phosphorylated CagA binds and activates C-terminal Src kinase (Csk) via its SH2 domain, which in turn inactivates the Src family of protein-tyrosine kinases. Since this signalling may induce apoptosis, the Csk pathway may attenuate the other CagA interactions.<sup>43</sup> In conclusion, attenuation of CagA activity by Csk may enable CagA-positive *HP* to infect the human stomach persistently for decades while avoiding excessive CagA toxicity to the host.<sup>43</sup> There is also evidence that CagA can be directly injected by T4SS inside B-lymphocytes. The delivered CagA induces the activation and stimulation of B cells (mediated by intracellular SHP-2 and phosphorylation of ERK and P38 MAPK), and could initiate the first step of transformation, also upregulating anti-apoptotic proteins BCL-2 and BCL-XL.<sup>44</sup> Moreover, Kuo and colleagues have demonstrated the presence of the bacterial protein CagA inside malignant B cells of MALT lymphoma and that those patients tend to respond faster to *HP* eradication.<sup>45</sup>

The vacuolating cytotoxin VacA, a high-molecular weight multimeric pore-forming protein is one of virulence factors produced by Hp and is responsible for epithelial cells by both apoptosis and programmed cell necrosis.<sup>46</sup> VacA forms a pore that permeabilizes the epithelial cell plasma membrane to urea,<sup>47</sup> that is an essential substrate for the *H. pylori*'s urease to mitigate acid gastric environment. More importantly, VacA determines immune suppression by blocking

phagosome maturation in macrophages,<sup>48</sup> inhibiting antigen presentation in T cells,<sup>49</sup> blocking T cell proliferation with down-regulation of Th1 effects through interaction with calcineurin to block intracellular signalling.<sup>50</sup>

Chronic *H. pylori* infection can trigger inflammation and immunological responses that stimulate lymphoid infiltration displaying features of classic MALT architecture.<sup>51</sup> It is suggested that *H. pylori* infection results in T-cell-dependent responses through the classic germinal centre reaction, with generation of reactive B and T cells; the *H. pylori*-specific T cells then migrate to the marginal zone/tumour area and provide non-cognate help to auto-reactive neoplastic B cells, which may involve stimulation of CD40 and other surface receptors by soluble ligands and cytokines.<sup>52,53</sup>

Host polymorphisms are also a crucial determinant of the interaction with *H. pylori* and could elucidate why only rarely MALT lymphoma develops. Determinants of host immune response variability have been extensively reviewed by Datta De<sup>36</sup> and mainly consist in variation in an inflammatory gene like IL-1 (*RN 2/2* genotype), glutathione S-transferase T1 null phenotype<sup>54</sup> and a negative association with HLA-B35.<sup>55</sup>

An important proof of concept of the association of Hp with Gastric MALT were the first report by Wotherspoon of MALT regression after successful eradication of Hp.<sup>56</sup> Those data have been corroborated by other studies,<sup>8,10</sup> thus fulfilling Hill's criteria of causality.

**Gastric MALT Beyond *Helicobacter Pylori*.** After a clonal expansion of B-cell *H. pylori*-driven has established in gastric mucosa, other mutational events can explain the gain of independence from the infection itself. Three chromosomal translocations are the most frequently detected t(11;18)(q21;q21)/API2-MALT1, t(1;14)(p22;q32)/BCL10-IGH, and t(14;18)(q32;q21)/IGH-MALT1, all converging to activation of nuclear factor kappa-B (NF- $\kappa$ B).<sup>53</sup> Translocation t(11;18)(q21;q21), occurring in approximately 30% of cases, fuses the N-terminus of the API2 gene to the C-terminus of the MALT1 gene and generates a functional API2-MALT1 fusion product,<sup>57,58</sup> the other two translocations involve translocation to immunoglobulin gene loci, and consequently increased expression, of BCL10 and MALT1 genes.<sup>12</sup> Gastric MALT lymphomas carrying the t(11;18) are more aggressive with spread to local lymph nodes<sup>59</sup> and, most importantly, rarely respond to HP eradication.<sup>60,61</sup> Therefore, its detection can influence the clinical management and is easily feasible with a commercial MALT1 dual-colour break-apart probe and an API2-MALT1 dual-colour dual-fusion probe for FISH, or by rt-PCR of the API2-MALT1

fusion mRNA transcripts.<sup>62</sup> Not translocated cases frequently carry trisomies of chromosomes 3, 12 and 18.<sup>63</sup>

**Gastric MALT lymphoma *H. Pylori* Negative.** Another interesting setting is represented by gastric MALT lymphoma, *H. pylori* negative that responded to antibiotic treatment in 15.5% of cases, despite *H. pylori* triple negativity test.<sup>64,65</sup> Those data have been interpreted by authors in light of a limited accuracy of *H. pylori* detection (false negative) or the possible presence of other unidentified bacteria implicated in MALT pathogenesis.<sup>65</sup> Nowadays, given the limited toxicity, low costs and risk of low-grade lymphoma progression, antibiotic therapy is also recommended in *H. pylori*- cases.<sup>66</sup>

**Antibiotic Treatment.** As previously discussed, targeting *H. pylori* seems a logical first line approach for gastric MALT lymphoma. Several effective schemes are available for the treatment of *H. pylori* infection.<sup>67-69</sup> The antibiotic choice should be based mainly on the epidemiology of Hp resistance to clarithromycin. Therefore, in countries with a prevalence >15% (That is the case of Europe, with the exception of Northern States)<sup>70</sup> antimicrobial susceptibility testing could be useful.<sup>18</sup> The most commonly used regimen is triple therapy: a proton pump inhibitor (omeprazole)<sup>71</sup> in association with amoxicillin and clarithromycin.<sup>72</sup> Metronidazole can be substituted to amoxicillin in penicillin-allergic individuals. An alternative is represented by the Sequential treatment, which includes a 5-day period with PPI+amoxicillin, followed by a 5-day period with PPI-clarithromycin-metronidazole.<sup>73</sup> For failure of the first line therapy or for clarithromycin-resistant isolated strains, it is available a bismuth-based quadruple therapy with omeprazole, bismuth salts, metronidazole and tetracycline (OBMT),<sup>74</sup> an RCT using a combination of PPI and a single three-in-one capsule tablet showed improved eradication in comparison with standard triple therapy.<sup>75</sup> Finally, in case of failure of the second-line treatment (bismuth-containing quadruple regimen), it is recommended to use the

PPI-levofloxacin-amoxicillin regimen,<sup>76,77</sup> always considering the rise in epidemiologic *H. pylori* resistance to levofloxacin.<sup>68</sup>

MALT lymphoma response to *H. pylori* eradication is about 80%.<sup>65</sup> However the length of time necessary to obtain a remission can span from few months to more than 12 months.

**Anti-Lymphoma Directed Treatment.** In cases not responding to antibiotic treatment, a control of localised disease can be achieved with radiation therapy alone with moderate-dose involved-field radiotherapy (24–30 Gy) to the stomach and perigastric nodes.<sup>13,78</sup>

Patients with the symptomatic systemic disease should be considered for systemic treatment that encompass the association of rituximab + chemotherapy. Rituximab in combination with chlorambucil has been proven in a randomised study by International Extranodal Lymphoma Study Group (IELSG)-19 where an excellent event-free-survival was achieved, superior to chlorambucil alone, although no overall survival benefit has been shown. Aggressive anthracycline-containing regimens (CHOP-like) are not usually necessary and should be reserved for cases with transformation to high grade.<sup>13</sup>

### **Marginal Zone Lymphoma and HCV.**

A heterogeneous group of lymphoproliferative disorders have been long suspected to be associated with HCV infection. HCV-related Mixed cryoglobulinemia (MC) is considered as a low-grade B-cell lymphoproliferative disorder, characterized clinically by arthritis, cutaneous vasculitis (palpable purpura), and, occasionally associated with glomerulonephritis and by the presence of circulating cryoprecipitable immune complexes of more than one immunoglobulin class. MC is defined by laboratory findings: the presence of serum Ig that precipitate at low temperatures (< 37°C) and can solve by warming serum, that are produced by the lymphoproliferation of B-cells clones secreting pathogenic IgM with rheumatoid factor activity. MC can evolve into an overt B-cell NHL in approximately 8–10% of cases after a long period.<sup>79</sup>

MZLs, in particular splenic (SMZL) and nodal MZL (NMZL), and other extranodal-MZL are the iNHL subtypes most frequently described as being HCV-related (80-82). SMZL is an indolent and rare entity, separately recognised by WHO,<sup>1,83</sup> usually presenting with symptomatic splenomegaly, cytopenias, autoimmune phenomena, and serum monoclonal paraprotein; in some patients a leukemic phase characterized by circulating lymphocytes with villous projections defines the so-called Splenic lymphoma with villous lymphocytes (SLVL).<sup>84</sup> SMZL, albeit rare, in a population-based study, has been reported with an incidence between 2001 and 2008 of 0.13 per 100,000 person-years, accounting for 0.6% of all NHL cases<sup>85</sup> and is the most common primary splenic lymphoma.<sup>86</sup> SMZL incidence is higher among older (median age is 65 years), white and male (male-to-female ratio of 1.2:1) population, in the United States.<sup>85</sup>

NMZL is a distinct clinical-pathological subtype of MZL characterized by exclusive primary lymph node localization in the absence of extranodal or splenic disease.<sup>1</sup> NMZLs represent only 1.5% to 1.8% of all lymphoid neoplasms; the most frequent clinical presentation is a generalized or, less frequently, localized lymphadenopathy.

Recently, Paulli et al. have reported a new subset of patients with extranodal HCV-related MZL characterized by a primary 'lipoma-like' subcutaneous presentation and an indolent clinical course.<sup>87</sup>

**Role of HCV in iNHL.** Hepatitis C virus (HCV) is an enveloped, RNA virus of the Flaviviridae family; it comprises six major genotypes, whose prevalence varies among different population and countries. HCV is not only hepatotropic, causing infection of hepatocytes associated with hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC), but is also responsible for other extrahepatic manifestations, of whose the most frequent is lymphoproliferation.<sup>88</sup>

**Models of Pathogenesis in HCV-Induced Lymphoproliferation.** The mechanisms underlying B-cell lymphoproliferation possibly induced, directly or indirectly, by HCV chronic infection are yet not fully understood. However, few experimental data suggest some clues to explain this phenomenon and have been reviewed elsewhere.<sup>89,90</sup>

The first observation derives from the HCV chronic antigenic stimulation leading to continuous stimulation and selection of reactive B-clones. HCV-associated NHLs derive from B cells activated during HCV infection, with some of these B cells being specific for the protein HCV-E2, which is the primary target of antibody responses against HCV.<sup>91</sup> Moreover, the monoclonal IgM component of type II MC is often encoded by the same set of Variable region genes, V<sub>H</sub>1-69, and V<sub>k</sub>3-A27 and similarly the same genes can be demonstrated to be involved in some cases of HCV-related NHL.<sup>92,93</sup> The burden of these data suggests that HCV-associated lymphomas are derived from clonally expanded B cells stimulated by HCV-E2 protein.

HCV is a positive, single-strand RNA virus, lacking a DNA intermediate in its replicative cycle. Thus, insertional mutagenesis in infected B-cells seems not possible. Moreover, there is conflicting evidence about the demonstration in B-cells of the negative RNA viral strand, which would be consistent with active viral replication. In fact, in a Japanese study negative-strand HCV RNA was detected in B cells only in 4 of the 75 (5%) patients<sup>94</sup> while no replicative intermediates were detected in another study.<sup>95</sup> In addition, B-cells could be not suitable for virus entry because claudin-1, a membrane co-receptor required for HCV infection is not present in peripheral blood cells.<sup>96</sup>

Conversely, more robust data exist supporting a direct B-cell stimulation by the engagement of CD81 on their surface by a combination of HCV-E2 and anti-CD81 antibodies leading to polyclonal activation of naïve, CD27- B-cells.<sup>97</sup>

**Antiviral Therapy.** Since 1990, several Epidemiologic studies suggested an association between hepatitis C

virus (HCV) infection and B-cell NHL, although with geographical heterogeneity due to the different prevalence of HCV seropositivity.<sup>98-102</sup> Nevertheless, many of these studies suffered from methodologic restrictions such as their retrospective nature, the consideration of prevalent instead of incident cases, missing or inappropriate controls. In 2003, the GIMEMA group published an Italian case-control study performed with adequate epidemiologic methods that demonstrated a clear association between HCV infection and various types of B-NHL.<sup>103</sup> Recently a larger case-control study of InterLymph NHL Subtypes Project hepatitis confirmed the increased risk of MZL in C virus seropositive patients (EMZL OR = 5.29, 95% CI = 2.48 to 11.28).<sup>104</sup> In 2002, Hermine et al. reported the first series of nine patients with SLVL in which a complete regression of lymphoma was obtained with antiviral treatment (AT) consisting of interferon (IFN) +/- ribavirin.<sup>105</sup> As a control, the authors reported 6 pts. with the same disease, but without HCV infection, not responding to the same treatment. This argument suggested for the first time that viral eradication and not the direct anti-proliferative effect of IFN was responsible for HCV-related NHL regression. Many single cases subsequently confirmed this observation, although, due to the rarity of HCV-related NHL, very few prospective studies have been published. In 20 patients, Vallisa et al. demonstrated a complete response to antiviral treatment of different subtypes in 70% of indolent i-NHL.<sup>106</sup> Recently a multicenter study of Fondazione Italiana Linfomi (FIL) recorded more than 700 patients with i-NHL and HCV seropositivity, demonstrating that AT used in the first line in 100 pts produced 44 CR and 33 PR.<sup>107</sup> A French prospective study of 116 HCV-positive patients with B-NHL revealed that within the MZL subgroup (n=45 pts.), 84% (n=38) received AT and 61% (n=23) achieved a Sustained Virological Response.<sup>108</sup> Moreover, outcome analysis showed a favourable association between OS and AT in MZL patients (P=0.04).<sup>108</sup> From these experiences, AT is, to date, considered the first-line approach for the cases of HCV-related indolent lymphoma, not requiring immediate chemo-immunotherapy. The recent introduction of new, highly active, antiviral treatments could clarify whether a pure antiviral approach,<sup>109-111</sup> free from the confounding role of interferon,<sup>112</sup> is equally or even more efficacious against lymphoma.

### Ocular Adnexa MALT Lymphoma.

Ocular adnexa MALT lymphoma (OAML), although uncommon, is the third most frequently involved site of MZL with an incidence rate of 1.4/1,000,000 person-years, with a median age of 65 years,<sup>6</sup> thus accounting for 50-78% of all ocular lymphomas in Western Countries.<sup>113</sup> Moreover, Danish and American SEER

data from surveillance registries have reported an increase in the incidence of OAML.<sup>114,115</sup> Clinical presentation of orbital fat lymphomas involvement (75% of OAML) includes exophthalmos (27% of cases), palpable mass (19%), eyelid ptosis (6%), diplopia (2%), eyelid nodule, orbital oedema, epiphora and a variable degree of impaired ocular motility, while the most common sign for conjunctival lymphomas (25% of OAML) is the characteristic 'salmon red patch'.<sup>116</sup> OAML is an indolent lymphoma with a favourable clinical outcome emphasized by a 10-year overall survival of 81%, with no deaths from lymphoma for the patients treated with radiotherapy<sup>117</sup> and 94% for the patients managed with 'watch and wait'.<sup>118</sup> Microscopically neoplastic cells are monocytoid, centrocytic-like or lymphoplasmocitoid and their immunophenotype is similar to that of other MALT lymphomas: CD20+, CD79a+, usually IgM+ with light-chain restriction, PAX5+, bcl-2+, TCL1+, CD11c+/-, CD43+/-, CD21+/-, CD35+/-, and IgD2, CD32, CD52, CD102, CD23-, cyclin D1-, bcl-6-, MUM1-.<sup>119</sup> Frequent chromosomal alteration encompasses trisomy 3 in 62% of cases and trisomy 18 in 47% of cases.<sup>120</sup> In addition, the most common translocations in ocular adnexal MALT lymphomas are the t(11;18)(q21;q21)/API2-MALT1 and the t(14;18)(q32;q21)/IGH-MALT1.<sup>121</sup> The immunoglobulin heavy-chain gene rearrangement is clonal in 55% of cases<sup>122</sup> and shows somatic hypermutation in two-thirds of these,<sup>123</sup> with a majority of selected genes commonly implicated in the assembly of autoantibodies, hence supporting the view that OAML represents a clonal expansion of post-germinal-centre memory B-cells, where selection may have occurred driven by antigen stimulation.<sup>123</sup> Moreover, in OAML a possible infectious association has been long proposed, *Chlamidophila spp.* and, to a lesser extent, *H. pylori* and HCV<sup>124</sup> have been proposed as causative agents. Although the association with *Hp* is controversial,<sup>125</sup> a more robust evidence is available for the role of *C. psittaci*.<sup>119,126</sup>

**Role of *C. Psittaci* in Ocular Adnexa MALT Lymphoma.** *Chlamydophila psittaci* (CP) is an obligate intracellular bacterium responsible for psittacosis/ornithosis in birds and in humans after zoonotic infection through inhalation of aerosolized bacteria when exposed to infected birds or handling contaminated feathers, faecal material or carcasses.<sup>127</sup> CP infection is commonly asymptomatic with repeated infection cycles in humans but mainly involves the respiratory tract. CP has been reported as a potential trigger for OAML, and Ferreri et colleagues firstly showed the efficacy of antibiotic treatment.<sup>126</sup> In this work CP DNA was found in lymphoma samples from 32 of the 40 (80%) case-patients analysed, thus revealing a strong association between OAML and CP

infection, also in light of the low seroprevalence in general population studies varying between 0 and 49% (median: 5–10%).<sup>128</sup> Moreover, Ponzoni et al. reported the presence of CP in 74% OAML specimens by different techniques such as immunohistochemistry, immunofluorescence and laser-capture microdissection-assisted PCR inside infiltrating monocytes/macrophages.<sup>129</sup> Nevertheless, significant variability in CP association with OAML has been reported in different geographical areas, ranging from 47% in Germany to 35% in the East Coast of the USA, 29% in the Netherlands, 13% in Italy, 12% in UK and 11% in Southern China,<sup>130</sup> while no evidence of CP infection was found in cases from the South Florida<sup>131</sup> and Japan.<sup>132</sup> To sum up, the overall prevalence of CP infection in 423 cases of OAML reported in 14 different papers is 19%.<sup>128</sup> In conclusion, the possible role of methodological pitfalls and other interpretation bias or confounding factors should be carefully considered when interpreting the bacteria-lymphoma association, also focussing on the potential role for *C. psittaci* infection in lymphomagenesis.<sup>128</sup>

**Treatment.** OAML is a rare indolent lymphoma, for its treatment no consensus is available because no prospective clinical trials have been conducted to define the optimal treatment approach for these patients.<sup>133</sup> However, patients managed by a watch & wait for approach have a 10-years OS of 94%.<sup>118</sup> Moreover, limited toxicity and costs associated with antibiotic treatment should suggest the opportunity to target the possibly correlated infection by *C. psittaci*, in analogy with gastric MALT lymphoma and *Hp* eradication. A single antibiotic course of oral doxycycline at a dose of 100 mg, given twice a day, for 3 weeks is the most popular regimen. In the first prospective trial of doxycycline, 20 of the 27 patients were progression free at 2 years; interestingly also 6 CP DNA-negative patients of the 16 treated experienced lymphoma regression.<sup>134</sup> A subsequent international prospective phase II trial was performed by IELSG: the prevalence of Cp positivity in OAML was 89%; in these naïve patients, after CP eradication, lymphoma regressed with an ORR of 65%, with 6 complete and 16 partial responses.<sup>135</sup> A larger Korean prospective trial, enrolling 90 patients, showed an ORR of 27%.<sup>136</sup> Actually, a new prospective study (IELSG 39) is enrolling patients (<http://www.ielsg.org/trialsonfr.html>). On the contrary, another retrospective study did not show any response,<sup>137</sup> even if the short median follow-up of 9 months could have hampered the proper assessment of response. Altogether, in 9 studies identified in the literature by Kiesewetter and Raderer, 131 patients were treated with doxycycline resulting in an ORR of 45%, with CR achieved in 23 patients (18%) and PR achieved by 36 pts. (27%) (138). An interesting Italian

work by Govi et al. showed the efficacy of administration of 500 mg clarithromycin, twice a day, for 6-months, in relapsed/refractory EMZL after treatment with doxycycline.<sup>139</sup> Over the anti-bacterial effect on unidentified pathogens, clarithromycin could exert a direct anti-proliferating effect on OAML. Patients who fail to respond to doxycycline therapy can be successfully salvaged with chemotherapy and/or radiotherapy.

**Anti-Lymphoma Directed Treatment.** Standard treatment is based on surgical resection of the single lesion. Radiotherapy is known as a treatment modality with a high local control rate for primary OAML.<sup>140,141</sup> However, orbital irradiation can induce complications such as cataracts, keratitis, dry eye syndrome, and retinopathy.<sup>142</sup> Even if no universally accepted radiation schedule is available, National Cancer Center Network guidelines recommend radiotherapy of 20 to 30 Gy for initial treatment of early-stage non-gastric MZL of all sites and reirradiation for locally recurrent disease.

Only limited data on chemotherapy for patients with OAML suggest different association and schedule. The oral agent chlorambucil is the most frequently used chemotherapy agent and has an extremely favourable toxicity. Complete responses are observed in 67% to 100% of patients; however, long-term outcome data suggest that local recurrence occurs in up to 29% of patients.<sup>143-146</sup> Only a few cases of OAML have been treated with rituximab as single-agent, demonstrating high activity in both newly diagnosed and relapsed disease, although early recurrence is common.<sup>147-150</sup> Also, the association of rituximab and chlorambucil has been tested with encouraging results.<sup>151</sup> CNS prophylaxis is not recommended since OAML rarely recurs to CNS.<sup>152</sup>

## Role of *Borrelia Burgdorferi* in Primary Cutaneous B-cell Lymphomas.

MZL of the skin has an incidence rate of 1.1/1,000,000 person-years<sup>6</sup> and is predominant among males across all ages. *B. burgdorferi* (*Bb*) infection has been associated with skin MZL in some cases in Europe, but not in the U.S., Asia and some parts of Europe, thereby challenging the aetiological role of this agent.<sup>153,154</sup> In particular, in *Bb* endemic areas such as the Scottish Highlands<sup>155</sup> or Austria,<sup>156</sup> cutaneous MZL patients have demonstrated *Borrelia* infection in up to 40% cases, while no association was detected in two Italian case series.<sup>157,158</sup> However, in a nonendemic region like France, *Bb* DNA was found in 19% of 16 cases with primary cutaneous MALT lymphoma.<sup>159</sup>

*Bb* infection might be associated with chronic antigen-driven lymphomagenesis in the skin, which is the port of entry of this gram-negative spirochete, through a bite from Ixodid tick and is also the

infectious agent of Lyme borreliosis.<sup>5,160</sup> Moreover, in late Lyme borreliosis, lymphocytes may infiltrate the dermis and produce the characteristic borrelia “lymphocytoma”, a cutaneous B-cell pseudolymphoma characterized by ‘top-heavy’, mixed-cell lymphoid infiltrate, usually accompanied by the formation of lymphoid follicles with germinal centres.<sup>161</sup> Lyme disease and primary cutaneous lymphoma may represent a continuous spectrum of pathological states viewed as a multistep progression from lymphocytoma to “pseudolymphoma” eventually leading to primary cutaneous B-cell Lymphoma, where evidence of B-cell monoclonality may help distinguish between the different stages of the disease.<sup>5</sup>

Discordant data exist about cutaneous MZL recession after antibiotic treatment of *Bb* infection (generally consisting of cephalosporins +/- tetracyclines) and are based on case reports.<sup>138</sup> In conclusion, *Bb* and its association with cutaneous MZL are currently the object of investigation, even if an antibiotic treatment may be attempted given the indolent nature of the disease.<sup>162</sup>

## Concluding Remarks.

Marginal zone lymphoma is a fascinating clinical setting in which it has been clearly shown in several trials (see **Table 1**) that several therapies targeting the putative oncogenic infectious agent can induce steady lymphoma regression. It represents the proof of concept that a chronic stimulus on the immune system induced by an infectious agent, under particular host predisposition, may lead to the selection of abnormal B-clones and a more selection may result in overt lymphoma development. For gastric and the ocular adnexa MALT lymphomas the compelling evidence, to date, provides a rationale to implement actively antibiotics regimens that can be an effective first-line treatment due to the peculiar indolent course of the disease and the high therapeutic index of these drugs. Indeed, international guidelines state that “*Helicobacter pylori* eradication therapy must be given to all gastric MALT lymphomas, independently of stage”. Conversely, in OAML and MZL of the skin antibiotic treatment remains investigational, given the questionable results of the former and the paucity of data for the latter clinical setting.

With the recent availability of new direct-acting antiviral agents for HCV infection, that promise a rapid and sustained virological response, there is increasing interest in their employment to treat HCV-related SMZL and NMZL; however, further studies are needed to assess this strategy. In conclusion, we hope new evidence can improve our understanding of the pathogenesis of lymphoma mediated by antigen-dependent infectious agents, thus enabling the

availability of other alternative and efficacious anti- lymphoma treatments.

**Table 1.** Most relevant studies evaluating the efficacy of anti-infectious therapy for MZL regression.

Reference	Disease	Year	Patients	Antibacterial/Antiviral therapy	ORR	Response	Median follow-up (range) in months
Wundish T <sup>163</sup>	Gastric MALT	2005	120	<i>First line:</i> amoxicillin + omeprazole for 2 weeks <i>Second line:</i> metronidazole + omeprazole + clarithromycin for 10 days	90%	CR 96 (80%) PR 13 (10%) SD 11 (9%)	75 (2-116)
Kim JS <sup>164</sup>	Gastric MALT	2007	111	<i>First line:</i> omeprazole + amoxicillin + clarithromycin <i>Second line:</i> omeprazole + bismuthate + metronidazole + tetracycline	85%	CR 84 out of 99 cases (84.8%) SD 15 out of 99 cases (15.2%)	41 (11-125)
Raderer M <sup>165</sup>	Gastric MALT <i>H pylori</i> Negative	2015	24 (13)	Clarithromycin in all patients, +/- metronidazole +/- amoxicillin +PPI	46%	CR 5 (38%) PR 1 (7%) SD 4 (31%) PD 3 (23%)	95 (42-181)
Arcaini L <sup>107</sup>	SMZL 27% MALT 22%	2014	134	IFN (47) (IFN+RBV 36) peg-IFN 87 (IFN+RBV in 82)	77%	<i>First line:</i> CR 44 (44%) PR 33(33%) SD 14(14%)	NA
Michot JM <sup>108</sup>	MZL 39% DLBCL 39%	2015	45	Peg-interferon $\alpha$ + ribavirin In 6 pts peg-IFN+RBN+protease inhibitor	AT 78%  AT-R 100%	AT only 14pts CR 8 PR 3 AT+R 8 pts CR 3 PR 5	31 (19-71)
Han JJ <sup>136</sup>	OAML	2015	90	Doxycycline (100 mg bid) for 3 weeks	27%	CR 24(27%) SD 34(37%) PD 31(34%)	40.5 (8-85)
Ferreri AJ <sup>135</sup>	OAML	2012	34	Doxycycline 100 mg bid for 3 weeks	65%	CR 6 (18%) PR 16 (47%) SD 11 (32%) PD 1 (3%)	37 (15-62)
Govi S <sup>139</sup>	OAML	2010	11	Clarithromycin 500 mg bid for 6 months	45%	CR 2 (18%) PR 3 (27%) SD 3 (27%) PD 3 (27%)	25 (12-35)

R: rituximab, PPI: proton-pump inhibitors

## References:

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.
2. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, et al. Lymphoma incidence, survival and prevalence 2004-2014: subtype analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer.* 2015;112(9):1575-84. <http://dx.doi.org/10.1038/bjc.2015.94> PMID:25867256 PMID:PMC4453686
3. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood.* 2006;107(1):265-76. <http://dx.doi.org/10.1182/blood-2005-06-2508> PMID:16150940 PMID:PMC1895348
4. Wohrer S, Troch M, Streubel B, Zwerina J, Skrabcs C, Formanek M, et al. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. *Leukemia.* 2007;21(8):1812-8. <http://dx.doi.org/10.1038/sj.leu.2404782> PMID:17554381
5. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. *Blood.* 2006;107(8):3034-44. <http://dx.doi.org/10.1182/blood-2005-09-3679> PMID:16397126
6. Khalil MO, Morton LM, Devesa SS, Check DP, Curtis RE, Weisenburger DD, et al. Incidence of marginal zone lymphoma in the United States, 2001-2009 with a focus on primary anatomic site. *Br J Haematol.* 2014;165(1):67-77. <http://dx.doi.org/10.1111/bjh.12730> PMID:24417667 PMID:PMC3967856
7. Weber DM, Dimopoulos MA, Anandu DP, Pugh WC, Steinbach G. Regression of gastric lymphoma of mucosa-associated lymphoid tissue with antibiotic therapy for *Helicobacter pylori*. *Gastroenterology.* 1994;107(6):1835-8. PMID:7958698
8. Zullo A, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol.* 2010;8(2):105-10. <http://dx.doi.org/10.1016/j.cgh.2009.07.017> PMID:19631287
9. Gisbert JP, Calvet X. Review article: common misconceptions in the management of *Helicobacter pylori*-associated gastric MALT-lymphoma. *Aliment Pharmacol Ther.* 2011;34(9):1047-62. <http://dx.doi.org/10.1111/j.1365-2036.2011.04839.x> PMID:21919927
10. Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, et al. 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(4):507-13.



- <http://dx.doi.org/10.1136/gutjnl-2011-300495> PMID:21890816
11. Psyrris A, Papageorgiou S, Economopoulos T. Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management. *Ann Oncol.* 2008;19(12):1992-9. <http://dx.doi.org/10.1093/annonc/mdn525> PMID:18647965 PMCid:PMC2733120
  12. Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. *Nat Rev Cancer.* 2004;4(8):644-53. <http://dx.doi.org/10.1038/nrc1409> PMID:15286744
  13. Zucca E, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi144-8. <http://dx.doi.org/10.1093/annonc/mdt343> PMID:24078657
  14. Isaacson P, Chott A, Nakamura S, Muller-Hermelink H, Harris N, Swerdlow S. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Press I, editor. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4th ed. Lyon, France 2008. p. 214-7.
  15. Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol.* 2013;24(4):857-77. <http://dx.doi.org/10.1093/annonc/mds643> PMID:23425945
  16. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet.* 1984;1(8390):1311-5. [http://dx.doi.org/10.1016/S0140-6736\(84\)91816-6](http://dx.doi.org/10.1016/S0140-6736(84)91816-6)
  17. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med.* 1991;325(16):1127-31. <http://dx.doi.org/10.1056/NEJM199110173251603> PMID:1891020
  18. Mégraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev.* 2007;20(2):280-322. <http://dx.doi.org/10.1128/CMR.00033-06> PMID:17428887 PMCid:PMC1865594
  19. Morgner A, Schmelz R, Thiede C, Stolte M, Miehke S. Therapy of gastric mucosa associated lymphoid tissue lymphoma. *World J Gastroenterol.* 2007;13(26):3554-66. <http://dx.doi.org/10.3748/wjg.v13.i26.3554> PMID:17659705 PMCid:PMC4146794
  20. Xu W, Zhou C, Zhang G, Wang H, Wang L, Guo J. Repeating gastric biopsy for accuracy of gastric lymphoma diagnosis. *Gastroenterol Nurs.* 2010;33(4):313-7. <http://dx.doi.org/10.1097/SGA.0b013e3181ea9035> PMID:20679784
  21. Eck M, Greiner A, Schmausser B, Eck H, Kolve M, Fischbach W, et al. Evaluation of Helicobacter pylori in gastric MALT-type lymphoma: differences between histologic and serologic diagnosis. *Mod Pathol.* 1999;12(12):1148-51. PMID:10619268
  22. Eck M, Schmausser B, Greiner A, Muller-Hermelink HK. Helicobacter pylori in gastric mucosa-associated lymphoid tissue type lymphoma. *Recent Results Cancer Res.* 2000;156:9-18. [http://dx.doi.org/10.1007/978-3-642-57054-4\\_2](http://dx.doi.org/10.1007/978-3-642-57054-4_2) PMID:10802858
  23. Blaser MJ. Helicobacters are indigenous to the human stomach: duodenal ulceration is due to changes in gastric microecology in the modern era. *Gut.* 1998;43(5):721-7. <http://dx.doi.org/10.1136/gut.43.5.721> PMID:9824358 PMCid:PMC1727310
  24. Ghose C, Perez-Perez GI, Dominguez-Bello MG, Pride DT, Bravi CM, Blaser MJ. East Asian genotypes of Helicobacter pylori strains in Amerindians provide evidence for its ancient human carriage. *Proc Natl Acad Sci U S A.* 2002;99(23):15107-11. <http://dx.doi.org/10.1073/pnas.242574599> PMID:12417749 PMCid:PMC137551
  25. Blaser MJ, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest.* 2004;113(3):321. <http://dx.doi.org/10.1172/JCI20925> PMID:14755326 PMCid:PMC324548
  26. Kennemann L, Didelot X, Aebischer T, Kuhn S, Drescher B, Droge M, et al. Helicobacter pylori genome evolution during human infection. *Proceedings of the National Academy of Sciences.* 2011;108(12):5033-8. <http://dx.doi.org/10.1073/pnas.1018444108> PMID:21383187 PMCid:PMC3064335
  27. Björkholm B, Sjölund M, Falk PG, Berg OG, Engstrand L, Andersson DI. Mutation frequency and biological cost of antibiotic resistance in Helicobacter pylori. *Proceedings of the National Academy of Sciences.* 2001;98(25):14607-12. <http://dx.doi.org/10.1073/pnas.241517298> PMID:11717398 PMCid:PMC64729
  28. Suerbaum S, Josenhans C. Helicobacter pylori evolution and phenotypic diversification in a changing host. *Nature reviews microbiology.* 2007;5(6):441-52. <http://dx.doi.org/10.1038/nrmicro1658> PMID:17505524
  29. Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum.* 1994;61:1-241. PMID:7715068
  30. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer.* 2006;118(12):3030-44. <http://dx.doi.org/10.1002/ijc.21731> PMID:16404738
  31. Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med.* 2002;347(15):1175-86. <http://dx.doi.org/10.1056/NEJMra020542> PMID:12374879
  32. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med.* 2001;345(11):784-9. <http://dx.doi.org/10.1056/NEJMoa001999> PMID:11556297
  33. Holcombe C. Helicobacter pylori: the African enigma. *Gut.* 1992;33(4):429-31. <http://dx.doi.org/10.1136/gut.33.4.429> PMID:1582581 PMCid:PMC1374052
  34. Doglioni C, Wotherspoon AC, Moschini A, de Boni M, Isaacson PG. High incidence of primary gastric lymphoma in northeastern Italy. *Lancet.* 1992;339(8797):834-5. [http://dx.doi.org/10.1016/0140-6736\(92\)90280-G](http://dx.doi.org/10.1016/0140-6736(92)90280-G)
  35. Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, et al. An African origin for the intimate association between humans and Helicobacter pylori. *Nature.* 2007;445(7130):915-8. <http://dx.doi.org/10.1038/nature05562> PMID:17287725 PMCid:PMC1847463
  36. Datta De D, Roychoudhury S. To be or not to be: The host genetic factor and beyond in Helicobacter pylori mediated gastro-duodenal diseases. *World J Gastroenterol.* 2015;21(10):2883-95. <http://dx.doi.org/10.3748/wjg.v21.i10.2883> PMID:25780285 PMCid:PMC4356907
  37. Cover TL, Dooley CP, Blaser MJ. Characterization of and human serologic response to proteins in Helicobacter pylori broth culture supernatants with vacuolizing cytotoxin activity. *Infect Immun.* 1990;58(3):603-10. PMID:2307514 PMCid:PMC258508
  38. Crabtree JE, Taylor JD, Wyatt JI, Heatley RV, Shallcross TM, Tompkins DS, et al. Mucosal IgA recognition of Helicobacter pylori 120 kDa protein, peptic ulceration, and gastric pathology. *Lancet.* 1991;338(8763):332-5. [http://dx.doi.org/10.1016/0140-6736\(91\)90477-7](http://dx.doi.org/10.1016/0140-6736(91)90477-7)
  39. Blaser MJ, Perez-Perez GI, Kleanthous H, Cover TL, Peek RM, Chyou PH, et al. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res.* 1995;55(10):2111-5. PMID:7743510
  40. Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. *Science.* 2000;287(5457):1497-500. <http://dx.doi.org/10.1126/science.287.5457.1497> PMID:10688800
  41. Yamazaki S, Yamakawa A, Ito Y, Ohtani M, Higashi H, Hatakeyama M, et al. The CagA protein of Helicobacter pylori is translocated into epithelial cells and binds to SHP-2 in human gastric mucosa. *J Infect Dis.* 2003;187(2):334-7. <http://dx.doi.org/10.1086/367807> PMID:12552462
  42. Mimuro H, Suzuki T, Tanaka J, Asahi M, Haas R, Sasakawa C. Grb2 is a key mediator of helicobacter pylori CagA protein activities. *Mol Cell.* 2002;10(4):745-55. [http://dx.doi.org/10.1016/S1097-2765\(02\)00681-0](http://dx.doi.org/10.1016/S1097-2765(02)00681-0)
  43. Tsutsumi R, Higashi H, Higuchi M, Okada M, Hatakeyama M. Attenuation of Helicobacter pylori CagA x SHP-2 signaling by interaction between CagA and C-terminal Src kinase. *J Biol Chem.* 2003;278(6):3664-70. <http://dx.doi.org/10.1074/jbc.M208155200> PMID:12446738
  44. Lin WC, Tsai HF, Kuo SH, Wu MS, Lin CW, Hsu PI, et al. Translocation of Helicobacter pylori CagA into Human B lymphocytes, the origin of mucosa-associated lymphoid tissue lymphoma. *Cancer Res.* 2010;70(14):5740-8. <http://dx.doi.org/10.1158/0008-5472.CAN-09-4690> PMID:20587516
  45. Kuo SH, Chen LT, Lin CW, Wu MS, Hsu PN, Tsai HJ, et al.

- Detection of the *Helicobacter pylori* CagA protein in gastric mucosa-associated lymphoid tissue lymphoma cells: clinical and biological significance. *Blood Cancer Journal*. 2013;3(7):e125. <http://dx.doi.org/10.1038/bcj.2013.22> PMID:23852160 PMCid:PMC3730200
46. de Bernard M, Josenhans C. Pathogenesis of *Helicobacter pylori* infection. *Helicobacter*. 2014;19 Suppl 1:11-8. <http://dx.doi.org/10.1111/hel.12160> PMID:25167940
  47. Tombola F, Morbiato L, Del Giudice G, Rappuoli R, Zoratti M, Papini E. The *Helicobacter pylori* VacA toxin is a urea permease that promotes urea diffusion across epithelia. *J Clin Invest*. 2001;108(6):929-37. <http://dx.doi.org/10.1172/JCI13045> PMID:11560962 PMCid:PMC200932
  48. Zheng PY, Jones NL. *Helicobacter pylori* strains expressing the vacuolating cytotoxin interrupt phagosome maturation in macrophages by recruiting and retaining TACO (coronin 1) protein. *Cell Microbiol*. 2003;5(1):25-40. <http://dx.doi.org/10.1046/j.1462-5822.2003.00250.x>
  49. Molinari M, Salio M, Galli C, Norais N, Rappuoli R, Lanzavecchia A, et al. Selective inhibition of Ii-dependent antigen presentation by *Helicobacter pylori* toxin VacA. *J Exp Med*. 1998;187(1):135-40. <http://dx.doi.org/10.1084/jem.187.1.135> PMID:9419220 PMCid:PMC2199184
  50. Gebert B, Fischer W, Weiss E, Hoffmann R, Haas R. *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. *Science*. 2003;301(5636):1099-102. <http://dx.doi.org/10.1126/science.1086871> PMID:12934009
  51. Bamford KB, Fan X, Crowe SE, Leary JF, Gourley WK, Luthra GK, et al. Lymphocytes in the human gastric mucosa during *Helicobacter pylori* have a T helper cell 1 phenotype. *Gastroenterology*. 1998;114(3):482-92. [http://dx.doi.org/10.1016/S0016-5085\(98\)70531-1](http://dx.doi.org/10.1016/S0016-5085(98)70531-1)
  52. Craig VJ, Cogliatti SB, Arnold I, Gerke C, Balandat JE, Wundisch T, et al. B-cell receptor signaling and CD40 ligand-independent T cell help cooperate in *Helicobacter*-induced MALT lymphomagenesis. *Leukemia*. 2010;24(6):1186-96. <http://dx.doi.org/10.1038/leu.2010.76> PMID:20428202
  53. Du MQ. MALT lymphoma: many roads lead to nuclear factor-kappaB activation. *Histopathology*. 2011;58(1):26-38. <http://dx.doi.org/10.1111/j.1365-2559.2010.03699.x> PMID:21261681
  54. Rollinson S, Levene AP, Mensah FK, Roddam PL, Allan JM, Diss TC, et al. Gastric marginal zone lymphoma is associated with polymorphisms in genes involved in inflammatory response and antioxidative capacity. *Blood*. 2003;102(3):1007-11. <http://dx.doi.org/10.1182/blood-2002-12-3803> PMID:12676777
  55. Reimer P, Fischbach W, Goebeler ME, Kraus MR, Goldmann S, Muller C, et al. Decreased frequency of HLA-B35 in patients with gastric MALT lymphoma. *Ann Hematol*. 2004;83(4):232-6. <http://dx.doi.org/10.1007/s00277-003-0809-8> PMID:14634793
  56. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet*. 1993;342(8871):575-7. [http://dx.doi.org/10.1016/0140-6736\(93\)91409-F](http://dx.doi.org/10.1016/0140-6736(93)91409-F)
  57. Akagi T, Motegi M, Tamura A, Suzuki R, Hosokawa Y, Suzuki H, et al. A novel gene, MALT1 at 18q21, is involved in t(11;18)(q21;q21) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Oncogene*. 1999;18(42):5785-94. <http://dx.doi.org/10.1038/sj.onc.1203018> PMID:10523859
  58. Dierlamm J, Baens M, Wlodarska I, Stefanova-Ouzounova M, Hernandez JM, Hossfeld DK, et al. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood*. 1999;93(11):3601-9. PMID:10339464
  59. Liu H, Ye H, Dogan A, Ranaldi R, Hamoudi RA, Bearzi I, et al. T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. *Blood*. 2001;98(4):1182-7. <http://dx.doi.org/10.1182/blood.V98.4.1182> PMID:11493468
  60. Nakamura S, Ye H, Bacon CM, Goatly A, Liu H, Banham AH, et al. Clinical impact of genetic aberrations in gastric MALT lymphoma: a comprehensive analysis using interphase fluorescence in situ hybridisation. *Gut*. 2007;56(10):1358-63. <http://dx.doi.org/10.1136/gut.2007.123729> PMID:17525089 PMCid:PMC2000261
  61. Liu H, Ye H, Ruskone-Fourmestreaux A, De Jong D, Pileri S, Thiede C, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to *H. pylori* eradication. *Gastroenterology*. 2002;122(5):1286-94. <http://dx.doi.org/10.1053/gast.2002.33047> PMID:11984515
  62. Du MQ, Atherton JC. Molecular subtyping of gastric MALT lymphomas: implications for prognosis and management. *Gut*. 2006;55(6):886-93. <http://dx.doi.org/10.1136/gut.2004.061663> PMID:16698756 PMCid:PMC1856234
  63. Streubel B, Simonitsch-Klupp I, Mullauer L, Lamprecht A, Huber D, Siebert R, et al. Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. *Leukemia*. 2004;18(10):1722-6. <http://dx.doi.org/10.1038/sj.leu.2403501> PMID:15356642
  64. 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(17):2158-62. <http://dx.doi.org/10.3748/wjg.v16.i17.2158> PMID:20440857 PMCid:PMC2864842
  65. Zullo A, Hassan C, Ridola L, De Francesco V, Rossi L, Tomao S, et al. Eradication therapy in *Helicobacter pylori*-negative, gastric low-grade mucosa-associated lymphoid tissue lymphoma patients: a systematic review. *J Clin Gastroenterol*. 2013;47(10):824-7. <http://dx.doi.org/10.1097/MCG.0b013e318286ff72> PMID:23442842
  66. Ruskone-Fourmestreaux A, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, et al. EGLS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut*. 2011;60(6):747-58. <http://dx.doi.org/10.1136/gut.2010.224949> PMID:21317175
  67. Fuccio L, Laterza L, Zagari RM, Cennamo V, Grilli D, Bazzoli F. Treatment of *Helicobacter pylori* infection. *BMJ*. 2008;337:a1454. <http://dx.doi.org/10.1136/bmj.a1454> PMID:18794181
  68. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report. *Gut*. 2012;61(5):646-64. <http://dx.doi.org/10.1136/gutjnl-2012-302084> PMID:22491499
  69. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-25. <http://dx.doi.org/10.1111/j.1572-0241.2007.01393.x> PMID:17608775
  70. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2013;62(1):34-42. <http://dx.doi.org/10.1136/gutjnl-2012-302254> PMID:22580412
  71. Borody TJ, Andrews P, Fracchia G, Brandl S, Shortis NP, Bae H. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. *Gut*. 1995;37(4):477-81. <http://dx.doi.org/10.1136/gut.37.4.477> PMID:7489931 PMCid:PMC1382896
  72. Bazzoli F, Zagari RM, Fossi S, Pozzato P, Alampi G, Simoni P, et al. Short-term low-dose triple therapy for the eradication of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol*. 1994;6(9):773-8. <http://dx.doi.org/10.1097/00042737-199409000-00004>
  73. Gisbert JP, Calvet X, O'Connor A, Megraud F, O'Morain CA. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44(5):313-25. <http://dx.doi.org/10.1097/mcg.0b013e3181c8a1a3>
  74. de Boer WA, Driessen WM, Potters VP, Tytgat GN. Randomized study comparing 1 with 2 weeks of quadruple therapy for eradicating *Helicobacter pylori*. *Am J Gastroenterol*. 1994;89(11):1993-7. PMID:7942724
  75. Malfertheiner P, Bazzoli F, Delchier JC, Celinski K, Giguere M, Riviere M, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet*. 2011;377(9769):905-13. [http://dx.doi.org/10.1016/S0140-6736\(11\)60020-2](http://dx.doi.org/10.1016/S0140-6736(11)60020-2)
  76. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther*. 2006;23(1):35-44. <http://dx.doi.org/10.1111/j.1365-2036.2006.02737.x> PMID:16393278
  77. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol*. 2006;101(3):488-96. <http://dx.doi.org/10.1111/j.1572-0241.2006.00637.x>

- PMid:16542284
78. Wirth A, Gospodarowicz M, Aleman BM, Bressel M, Ng A, Chao M, et al. Long-term outcome for gastric marginal zone lymphoma treated with radiotherapy: a retrospective, multi-centre, International Extranodal Lymphoma Study Group study. *Ann Oncol.* 2013;24(5):1344-51. <http://dx.doi.org/10.1093/annonc/mds623> PMID:23293112
  79. Ferri C, Sebastiani M, Giuggioli D, Cazzato M, Longombardo G, Antonelli A, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin Arthritis Rheum.* 2004;33(6):355-74. <http://dx.doi.org/10.1016/j.semarthrit.2003.10.001> PMID:15190522
  80. Libra M, Polesel J, Russo AE, De Re V, Cina D, Serraino D, et al. Extrahepatic disorders of HCV infection: a distinct entity of B-cell neoplasia? *Int J Oncol.* 2010;36(6):1331-40. <http://dx.doi.org/10.3892/ijo.00000618> PMID:20428756
  81. Saadoun D, Suarez F, Lefrere F, Valensi F, Mariette X, Aouba A, et al. Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? *Blood.* 2005;105(1):74-6. <http://dx.doi.org/10.1182/blood-2004-05-1711> PMID:15353484
  82. Arcaini L, Burcheri S, Rossi A, Paulli M, Bruno R, Passamonti F, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. *Ann Oncol.* 2007;18(2):346-50. <http://dx.doi.org/10.1093/annonc/mdl388> PMID:17071937
  83. Schmid C, Kirkham N, Diss T, Isaacson PG. Splenic marginal zone cell lymphoma. *Am J Surg Pathol.* 1992;16(5):455-66. <http://dx.doi.org/10.1097/0000478-199205000-00004> PMID:1599024
  84. Matutes E, Morilla R, Owusu-Ankomah K, Houlihan A, Catovsky D. The immunophenotype of splenic lymphoma with villous lymphocytes and its relevance to the differential diagnosis with other B-cell disorders. *Blood.* 1994;83(6):1558-62. PMID:8123845
  85. Liu L, Wang H, Chen Y, Rustveld L, Liu G, Du XL. Splenic marginal zone lymphoma: a population-based study on the 2001-2008 incidence and survival in the United States. *Leuk Lymphoma.* 2013;54(7):1380-6. <http://dx.doi.org/10.3109/10428194.2012.743655> PMID:23101590
  86. Kraus MD, Fleming MD, Vonderheide RH. The spleen as a diagnostic specimen. *Cancer.* 2001;91(11):2001-9. [http://dx.doi.org/10.1002/1097-0142\(20010601\)91:11<2001::AID-CNCR1225>3.0.CO;2-3](http://dx.doi.org/10.1002/1097-0142(20010601)91:11<2001::AID-CNCR1225>3.0.CO;2-3)
  87. Paulli M, Arcaini L, Lucioni M, Boveri E, Capello D, Passamonti F, et al. Subcutaneous 'lipoma-like' B-cell lymphoma associated with HCV infection: a new presentation of primary extranodal marginal zone B-cell lymphoma of MALT. *Ann Oncol.* 2010;21(6):1189-95. <http://dx.doi.org/10.1093/annonc/mdp454> PMID:19858084
  88. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis.* 2007;39(1):2-17. <http://dx.doi.org/10.1016/j.dld.2006.06.008> PMID:16884964
  89. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood.* 2011;117(6):1792-8. <http://dx.doi.org/10.1182/blood-2010-06-275818> PMID:20959600
  90. Landau DA, Saadoun D, Calabrese LH, Cacoub P. The pathophysiology of HCV induced B-cell clonal disorders. *Autoimmun Rev.* 2007;6(8):581-7. <http://dx.doi.org/10.1016/j.autrev.2007.03.010> PMID:17854753
  91. Lesniewski R, Okasinski G, Carrick R, Van Sant C, Desai S, Johnson R, et al. Antibody to hepatitis C virus second envelope (HCV-E2) glycoprotein: a new marker of HCV infection closely associated with viremia. *J Med Virol.* 1995;45(4):415-22. <http://dx.doi.org/10.1002/jmv.1890450411> PMID:7545212
  92. Quinn ER, Chan CH, Hadlock KG, Fong SK, Flint M, Levy S. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. *Blood.* 2001;98(13):3745-9. <http://dx.doi.org/10.1182/blood.V98.13.3745> PMID:11739181
  93. Chan CH, Hadlock KG, Fong SK, Levy S. V(H)1-69 gene is preferentially used by hepatitis C virus-associated B cell lymphomas and by normal B cells responding to the E2 viral antigen. *Blood.* 2001;97(4):1023-6. <http://dx.doi.org/10.1182/blood.V97.4.1023> PMID:11159532
  94. Inokuchi M, Ito T, Uchikoshi M, Shimozuma Y, Morikawa K, Nozawa H, et al. Infection of B cells with hepatitis C virus for the development of lymphoproliferative disorders in patients with chronic hepatitis C. *J Med Virol.* 2009;81(4):619-27. <http://dx.doi.org/10.1002/jmv.21388> PMID:19235854
  95. Lanford RE, Chavez D, Chisari FV, Sureau C. Lack of detection of negative-strand hepatitis C virus RNA in peripheral blood mononuclear cells and other extrahepatic tissues by the highly strand-specific rTth reverse transcriptase PCR. *J Virol.* 1995;69(12):8079-83. PMID:7494326 PMCID:PMC189758
  96. Evans MJ, von Hahn T, Tschernig DM, Syder AJ, Panis M, Wolk B, et al. Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature.* 2007;446(7137):801-5. <http://dx.doi.org/10.1038/nature05654> PMID:17325668
  97. Rosa D, Saletti G, De Gregorio E, Zorat F, Comar C, D'Oro U, et al. Activation of naive B lymphocytes via CD81, a pathogenetic mechanism for hepatitis C virus-associated B lymphocyte disorders. *Proc Natl Acad Sci U S A.* 2005;102(51):18544-9. <http://dx.doi.org/10.1073/pnas.0509402102> PMID:16339892 PMCID:PMC1310512
  98. Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, et al. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. *Int J Cancer.* 2004;111(1):76-80. <http://dx.doi.org/10.1002/ijc.20021> PMID:15185346
  99. Ferri C, Caracciolo F, Zignego AL, Civita LL, Monti M, Longombardo G, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Br J Haematol.* 1994;88(2):392-4. <http://dx.doi.org/10.1111/j.1365-2141.1994.tb05036.x> PMID:7803287
  100. Mazzaro C, Zagonel V, Monfardini S, Tulissi P, Pussini E, Fanni M, et al. Hepatitis C virus and non-Hodgkin's lymphomas. *Br J Haematol.* 1996;94(3):544-50. <http://dx.doi.org/10.1046/j.1365-2141.1996.6912313.x> PMID:8790157
  101. Silvestri F, Barillari G, Fanin R, Salmasso F, Pipan C, Falasca E, et al. Impact of hepatitis C virus infection on clinical features, quality of life and survival of patients with lymphoplasmacytoid lymphoma/immunocytoma. *Ann Oncol.* 1998;9(5):499-504. <http://dx.doi.org/10.1023/A:1008265804550> PMID:9653490
  102. Sansonno D, De Vita S, Cornacchiulo V, Carbone A, Boiocchi M, Dammacco F. Detection and distribution of hepatitis C virus-related proteins in lymph nodes of patients with type II mixed cryoglobulinemia and neoplastic or non-neoplastic lymphoproliferation. *Blood.* 1996;88(12):4638-45. PMID:8977256
  103. Mele A, Pulsoni A, Bianco E, Musto P, Szklo A, Sampaolo MG, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. *Blood.* 2003;102(3):996-9. <http://dx.doi.org/10.1182/blood-2002-10-3230> PMID:12714514
  104. Bracci PM, Benavente Y, Turner JJ, Paltiel O, Slager SL, Vajdic CM, et al. Medical history, lifestyle, family history, and occupational risk factors for marginal zone lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr.* 2014;2014(48):52-65. <http://dx.doi.org/10.1093/jncimonographs/igu011> PMID:25174026 PMCID:PMC4207869
  105. Hermine O, Lefrere F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med.* 2002;347(2):89-94. <http://dx.doi.org/10.1056/NEJMoa013376> PMID:12110736
  106. Vallisa D, Bernuzzi P, Arcaini L, Sacchi S, Callea V, Marasca R, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol.* 2005;23(3):468-73. <http://dx.doi.org/10.1200/JCO.2005.06.008> PMID:15659492
  107. Arcaini L, Vallisa D, Rattotti S, Ferretti VV, Ferreri AJ, Bernuzzi P, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. *Ann Oncol.* 2014;25(7):1404-10. <http://dx.doi.org/10.1093/annonc/mdu166> PMID:24799461
  108. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. *Am J Hematol.* 2015;90(3):197-203. <http://dx.doi.org/10.1002/ajh.23889> PMID:25417909
  109. Sultanik P, Klotz C, Brault P, Pol S, Mallet V. Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment. *Blood.* 2015;125(15):2446-7. <http://dx.doi.org/10.1182/blood-2014-12-618652> PMID:25858892
  110. Cornberg M, Manns MP. New kids on the block--step by step to an

- ideal HCV therapy. *Lancet*. 2015;385(9973):1050-2. [http://dx.doi.org/10.1016/S0140-6736\(14\)62008-0](http://dx.doi.org/10.1016/S0140-6736(14)62008-0)
111. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med*. 2013;368(20):1907-17. <http://dx.doi.org/10.1056/NEJMra1213651> PMID:23675659 PMCID:PMC3893124
  112. Florian J, Mishra P, Arya V, Harrington P, Connelly S, Reynold KS, et al. Direct-acting antiviral drugs for the treatment of chronic hepatitis c virus infection: Interferon free is now. *Clin Pharmacol Ther*. 2015;n/a-n/a.
  113. Mannami T, Yoshino T, Oshima K, Takase S, Kondo E, Ohara N, et al. Clinical, Histopathological, and Immunogenetic Analysis of Ocular Adnexal Lymphoproliferative Disorders: Characterization of MALT Lymphoma and Reactive Lymphoid Hyperplasia. *Mod Pathol*. 0000;14(7):641-9. <http://dx.doi.org/10.1038/modpathol.3880366> PMID:11454995
  114. Moslehi R, Devesa SS, Schairer C, Fraumeni JF, Jr. Rapidly increasing incidence of ocular non-hodgkin lymphoma. *J Natl Cancer Inst*. 2006;98(13):936-9. <http://dx.doi.org/10.1093/jnci/djj248> PMID:16818858
  115. Sjo LD, Ralfkiaer E, Prause JU, Petersen JH, Madsen J, Pedersen NT, et al. Increasing incidence of ophthalmic lymphoma in Denmark from 1980 to 2005. *Invest Ophthalmol Vis Sci*. 2008;49(8):3283-8. <http://dx.doi.org/10.1167/iovs.08-1768> PMID:18390644
  116. Collina F, De Chiara A, De Renzo A, De Rosa G, Botti G, Franco R. Chlamydia psittaci in ocular adnexa MALT lymphoma: a possible role in lymphomagenesis and a different geographical distribution. *Infect Agent Cancer*. 2012;7:8. <http://dx.doi.org/10.1186/1750-9378-7-8> PMID:22472082 PMCID:PMC3355003
  117. Fung CY, Tarbell NJ, Lucarelli MJ, Goldberg SI, Linggood RM, Harris NL, et al. Ocular adnexal lymphoma: clinical behavior of distinct World Health Organization classification subtypes. *Int J Radiat Oncol Biol Phys*. 2003;57(5):1382-91. [http://dx.doi.org/10.1016/S0360-3016\(03\)00767-3](http://dx.doi.org/10.1016/S0360-3016(03)00767-3)
  118. Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Maruyama D, Kim SW, et al. Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma. *Ann Oncol*. 2006;17(1):135-40. <http://dx.doi.org/10.1093/annonc/mdj025> PMID:16236754
  119. Ferreri AJ, Dolcetti R, Du MQ, Doglioni C, Resti AG, Politi LS, et al. Ocular adnexal MALT lymphoma: an intriguing model for antigen-driven lymphomagenesis and microbial-targeted therapy. *Ann Oncol*. 2008;19(5):835-46. <http://dx.doi.org/10.1093/annonc/mdm513> PMID:17986622
  120. Tanimoto K, Sekiguchi N, Yokota Y, Kaneko A, Watanabe T, Maeshima AM, et al. Fluorescence in situ hybridization (FISH) analysis of primary ocular adnexal MALT lymphoma. *BMC Cancer*. 2006;6:249. <http://dx.doi.org/10.1186/1471-2407-6-249> PMID:17052360 PMCID:PMC1630703
  121. Ye H, Gong L, Liu H, Hamoudi RA, Shirali S, Ho L, et al. MALT lymphoma with t (14; 18)(q32; q21)/IGH - MALT1 is characterized by strong cytoplasmic MALT1 and BCL10 expression. *The Journal of pathology*. 2005;205(3):293-301. <http://dx.doi.org/10.1002/path.1715> PMID:15682443
  122. Mannami T, Yoshino T, Oshima K, Takase S, Kondo E, Ohara N, et al. Clinical, histopathological, and immunogenetic analysis of ocular adnexal lymphoproliferative disorders: characterization of malt lymphoma and reactive lymphoid hyperplasia. *Mod Pathol*. 2001;14(7):641-9. <http://dx.doi.org/10.1038/modpathol.3880366> PMID:11454995
  123. Coupland SE, Foss HD, Anagnostopoulos I, Hummel M, Stein H. Immunoglobulin VH gene expression among extranodal marginal zone B-cell lymphomas of the ocular adnexa. *Invest Ophthalmol Vis Sci*. 1999;40(3):555-62. PMID:10067957
  124. Ferreri AJ, Viale E, Guidoboni M, Resti AG, De Conciliis C, Politi L, et al. Clinical implications of hepatitis C virus infection in MALT-type lymphoma of the ocular adnexa. *Ann Oncol*. 2006;17(5):769-72. <http://dx.doi.org/10.1093/annonc/mdl027> PMID:16524978
  125. Goebel N, Serr A, Mittelviefhaus H, Reinhard T, Bogdan C, Auw-Haedrich C. Chlamydia psittaci, Helicobacter pylori and ocular adnexal lymphoma-is there an association? The German experience. *Leuk Res*. 2007;31(10):1450-2. <http://dx.doi.org/10.1016/j.leukres.2006.12.005> PMID:17257672
  126. Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell'Oro S, Fleischhauer K, et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. *J Natl Cancer Inst*. 2004;96(8):586-94. <http://dx.doi.org/10.1093/jnci/djh102> PMID:15100336
  127. Knittler MR, Sachse K. Chlamydia psittaci: update on an underestimated zoonotic agent. *Pathog Dis*. 2015;73(1):1-15. PMID:25853998
  128. Decaudin D, Dolcetti R, de Cremoux P, Ponzoni M, Vincent-Salomon A, Doglioni C, et al. Variable association between Chlamydia psittaci infection and ocular adnexal lymphomas: methodological biases or true geographical variations? *Anticancer Drugs*. 2008;19(8):761-5. <http://dx.doi.org/10.1097/CAD.0b013e32830b58c4> PMID:18690086
  129. Ponzoni M, Ferreri AJ, Guidoboni M, Lettini AA, Cangi MG, Pasini E, et al. Chlamydia infection and lymphomas: association beyond ocular adnexal lymphomas highlighted by multiple detection methods. *Clin Cancer Res*. 2008;14(18):5794-800. <http://dx.doi.org/10.1158/1078-0432.CCR-08-0676> PMID:18794089
  130. Chanudet E, Zhou Y, Bacon CM, Wotherspoon AC, Muller-Hermelink HK, Adam P, et al. Chlamydia psittaci is variably associated with ocular adnexal MALT lymphoma in different geographical regions. *J Pathol*. 2006;209(3):344-51. <http://dx.doi.org/10.1002/path.1984> PMID:16583361
  131. Rosado MF, Byrne GE, Ding F, Fields KA, Ruiz P, Dubovy SR, et al. Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with Chlamydia psittaci. *Blood*. 2006;107(2):467-72. <http://dx.doi.org/10.1182/blood-2005-06-2332> PMID:16166588 PMCID:PMC1895606
  132. Daibata M, Nemoto Y, Togitani K, Fukushima A, Ueno H, Ouchi K, et al. Absence of Chlamydia psittaci in ocular adnexal lymphoma from Japanese patients. *Br J Haematol*. 2006;132(5):651-2. <http://dx.doi.org/10.1111/j.1365-2141.2005.05943.x> PMID:16445841
  133. Stefanovic A, Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. *Blood*. 2009;114(3):501-10. <http://dx.doi.org/10.1182/blood-2008-12-195453> PMID:19372259 PMCID:PMC2713468
  134. Ferreri AJ, Ponzoni M, Guidoboni M, Resti AG, Politi LS, Cortelazzo S, et al. Bacteria-eradicating therapy with doxycycline in ocular adnexal MALT lymphoma: a multicenter prospective trial. *J Natl Cancer Inst*. 2006;98(19):1375-82. <http://dx.doi.org/10.1093/jnci/djj373> PMID:17018784
  135. Ferreri AJ, Govi S, Pasini E, Mappa S, Bertoni F, Zaja F, et al. Chlamydia psittaci eradication with doxycycline as first-line targeted therapy for ocular adnexal lymphoma: final results of an international phase II trial. *J Clin Oncol*. 2012;30(24):2988-94. <http://dx.doi.org/10.1200/JCO.2011.41.4466> PMID:22802315
  136. Han JJ, Kim TM, Jeon YK, Kim MK, Khwarg SI, Kim CW, et al. Long-term outcomes of first-line treatment with doxycycline in patients with previously untreated ocular adnexal marginal zone B cell lymphoma. *Ann Hematol*. 2015;94(4):575-81. <http://dx.doi.org/10.1007/s00277-014-2240-8> PMID:25338969
  137. Grunberger B, Hauff W, Lukas J, Wohrer S, Zielinski CC, Streubel B, et al. 'Blind' antibiotic treatment targeting Chlamydia is not effective in patients with MALT lymphoma of the ocular adnexa. *Ann Oncol*. 2006;17(3):484-7. <http://dx.doi.org/10.1093/annonc/mdj143> PMID:16500916
  138. Kiesewetter B, Raderer M. Antibiotic therapy in nongastrintestinal MALT lymphoma: a review of the literature. *Blood*. 2013;122(8):1350-7. <http://dx.doi.org/10.1182/blood-2013-02-486522> PMID:23770778
  139. Govi S, Dognini GP, Licata G, Crocchiolo R, Resti AG, Ponzoni M, et al. Six-month oral clarithromycin regimen is safe and active in extranodal marginal zone B-cell lymphomas: final results of a single-centre phase II trial. *Br J Haematol*. 2010;150(2):226-9. <http://dx.doi.org/10.1111/j.1365-2141.2010.08179.x>
  140. De Cicco L, Cella L, Liuzzi R, Solla R, Farella A, Punzo G, et al. Radiation therapy in primary orbital lymphoma: a single institution retrospective analysis. *Radiation Oncology*. 2009;4(1):60. <http://dx.doi.org/10.1186/1748-717X-4-60> PMID:19968864 PMCID:PMC2794866
  141. Nam H, Ahn Y, Kim Y, Ko Y, Kim W. Prognostic significance of anatomic subsites: results of radiation therapy for 66 patients with localized orbital marginal zone B cell lymphoma. *Radiother Oncol*. 2009;90:236 - 41. <http://dx.doi.org/10.1016/j.radonc.2008.09.011> PMID:18950885
  142. Cho WK, Lee SE, Paik JS, Cho SG, Yang SW. Risk potentiality of

- frontline radiotherapy associated cataract in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma. *Korean J Ophthalmol.* 2013;27(4):243-8. <http://dx.doi.org/10.3341/kjo.2013.27.4.243> PMID:23908569 PMCID:PMC3730065
- 143.Charlotte F, Doghmi K, Cassoux N, Ye H, Du M-Q, Kujas M, et al. Ocular adnexal marginal zone B cell lymphoma: a clinical and pathologic study of 23 cases. *Virchows Arch.* 2006;448(4):506-16. <http://dx.doi.org/10.1007/s00428-005-0122-0> PMID:16323006
- 144.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(7):1209-13. <http://dx.doi.org/10.1016/j.ophtha.2006.01.057> PMID:16647129
- 145.Song E-K, Kim S-Y, Kim TM, Lee K-W, Yun T, Na I-I, et al. Efficacy of chemotherapy as a first-line treatment in ocular adnexal extranodal marginal zone B-cell lymphoma. *Ann Oncol.* 2008;19(2):242-6. <http://dx.doi.org/10.1093/annonc/mdm457> PMID:17947227
- 146.Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Watanabe T, Kobayashi Y, et al. Primary Ocular Adnexal MALT Lymphoma: A Long-term Follow-up Study of 114 Patients. *Jpn J Clin Oncol.* 2007;37(5):337-44. <http://dx.doi.org/10.1093/jjco/hym031> PMID:17562719
- 147.Ferreri A, Ponzoni M, Martinelli G, Muti G, Guidoboni M, Dolcetti R, et al. Rituximab in patients with mucosal-associated lymphoid tissue-type lymphoma of the ocular adnexa. *Haematologica.* 2005;90(11):1578-9. PMID:16266908
- 148.Benetatos L, Alymara V, Asproudis I, Bourantas KL. Rituximab as first line treatment for MALT lymphoma of extraocular muscles. *Ann Hematol.* 2006;85(9):625-6. <http://dx.doi.org/10.1007/s00277-006-0134-0> PMID:16691396
- 149.Heinz C, Merz H, Nieschalk M, Mueller-Miny H, Koch P, Heiligenhaus A. Rituximab for the treatment of extranodal marginal zone B-cell lymphoma of the lacrimal gland. *Br J Ophthalmol.* 2007;91(11):1563-4. <http://dx.doi.org/10.1136/bjo.2007.115626> PMID:17947275 PMCID:PMC2095418
- 150.Zinzani PL, Alinari L, Stefoni V, Loffredo A, Pichierri P, Polito E. Rituximab in primary conjunctiva lymphoma. *Leuk Res.* 2005;29(1):107-8. <http://dx.doi.org/10.1016/j.leukres.2004.05.011> PMID:15541482
- 151.Rigacci L, Nassi L, Puccioni M, Mappa S, Polito E, Dal Pozzo S, et al. Rituximab and chlorambucil as first-line treatment for low-grade ocular adnexal lymphomas. *Ann Hematol.* 2007;86(8):565-8. <http://dx.doi.org/10.1007/s00277-007-0301-y> PMID:17483948
- 152.Restrepo A, Raez LE, Byrne GE, Jr., Johnson T, Ossi P, Benedetto P, et al. Is central nervous system prophylaxis necessary in ocular adnexal lymphoma? *Crit Rev Oncog.* 1998;9(3-4):269-73. PMID:10201631
- 153.Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood.* 2005;105(10):3768-85. <http://dx.doi.org/10.1182/blood-2004-09-3502> PMID:15692063
- 154.Takino H, Li C, Hu S, Kuo TT, Geissinger E, Muller-Hermelink HK, et al. Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathological study of cases from Asia, Germany, and the United States. *Mod Pathol.* 2008;21(12):1517-26. <http://dx.doi.org/10.1038/modpathol.2008.159> PMID:18820662
- 155.Goodlad JR, Davidson MM, Hollowood K, Ling C, MacKenzie C, Christie I, et al. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the Highlands of Scotland. *Am J Surg Pathol.* 2000;24(9):1279-85. <http://dx.doi.org/10.1097/0000478-200009000-00012> PMID:10976703
- 156.Cerroni L, Zochling N, Putz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. *J Cutan Pathol.* 1997;24(8):457-61. <http://dx.doi.org/10.1111/j.1600-0560.1997.tb01318.x> PMID:9331890
- 157.Ponzoni M, Ferreri AJ, Mappa S, Pasini E, Govi S, Facchetti F, et al. Prevalence of *Borrelia burgdorferi* infection in a series of 98 primary cutaneous lymphomas. *Oncologist.* 2011;16(11):1582-8. <http://dx.doi.org/10.1634/theoncologist.2011-0108> PMID:22071292 PMCID:PMC3233293
- 158.Goteri G, Ranaldi R, Simonetti O, Capretti R, Menzo S, Stramazotti D, et al. Clinicopathological features of primary cutaneous B-cell lymphomas from an academic regional hospital in central Italy: No evidence of *Borrelia burgdorferi* association. *Leuk Lymphoma.* 2007;48(11):2184-8. <http://dx.doi.org/10.1080/10428190701618250> PMID:17926178
- 159.de la Fouchardiere A, Vandenesch F, Berger F. *Borrelia*-associated primary cutaneous MALT lymphoma in a nonendemic region. *Am J Surg Pathol.* 2003;27(5):702-3. <http://dx.doi.org/10.1097/0000478-200305000-00017> PMID:12717258
- 160.Ferreri AJ, Govi S, Ponzoni M. Marginal zone lymphomas and infectious agents. *Semin Cancer Biol.* 2013;23(6):431-40. <http://dx.doi.org/10.1016/j.semcancer.2013.09.004> PMID:24090976
- 161.Colli C, Leinweber B, Müllegger R, Chott A, Kerl H, Cerroni L. *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. *J Cutan Pathol.* 2004;31(3):232-40. <http://dx.doi.org/10.1111/j.0303-6987.2003.00167.x> PMID:14984575
- 162.Zenahlik P, Fink-Puches R, Kapp KS, Kerl H, Cerroni L. [Therapy of primary cutaneous B-cell lymphomas]. *Hautarzt.* 2000;51(1):19-24. <http://dx.doi.org/10.1007/s001050050005> PMID:10663035
- 163.Wundisch T, Thiede C, Morgner A, Dempfle A, Gunther A, Liu H, et al. Long-term follow-up of gastric MALT lymphoma after *Helicobacter pylori* eradication. *J Clin Oncol.* 2005;23(31):8018-24. <http://dx.doi.org/10.1200/JCO.2005.02.3903> PMID:16204012
- 164.Kim JS, Chung SJ, Choi YS, Cheon JH, Kim CW, Kim SG, et al. *Helicobacter pylori* eradication for low-grade gastric mucosa-associated lymphoid tissue lymphoma is more successful in inducing remission in distal compared to proximal disease. *Br J Cancer.* 2007;96(9):1324-8. <http://dx.doi.org/10.1038/sj.bjc.6603708>
- 165.Raderer M, Wohrer S, Kiesewetter B, Dolak W, Lagler H, Wotherspoon A, et al. Antibiotic treatment as sole management of *Helicobacter pylori*-negative gastric MALT lymphoma: a single center experience with prolonged follow-up. *Ann Hematol.* 2015;94(6):969-73. <http://dx.doi.org/10.1007/s00277-014-2298-3> PMID:25579756