Emerging Role of Infectious Etiologies in the Pathogenesis of Marginal Zone B-cell Lymphomas

Emanuele Zucca¹, Francesco Bertoni¹,², Barbara Vannata¹, and Franco Cavalli¹

Abstract

Extranodal marginal zone B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT) arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. The most frequently affected organ is the stomach, where MALT lymphoma is incontrovertibly associated with a chronic gastritis induced by a microbial pathogen, Helicobacter pylori. Gastric MALT lymphoma therefore represents a paradigm for evaluating inflammation-associated lymphomagenesis, which may lead to a deeper understanding of a possible etiologic association between other microorganisms and nongastric marginal zone lymphomas. Besides infectious etiology, chronic inflammation caused by autoimmune diseases, such as Sjögren syndrome or Hashimoto thyroiditis, can also carry a significant risk factor for the development of marginal zone lymphoma. In addition to the continuous antigenic drive, additional oncogenic events play a relevant role in lymphoma growth and progression to the point at which the lymphoproliferative process may eventually become independent of antigenic stimulation. Recent studies on MALT lymphomas have in fact demonstrated genetic alterations affecting the NF-κB pathway, a major signaling pathway involved in many cancers. This review aims to present marginal zone lymphoma as an example of the close pathogenetic link between chronic inflammation and tumor development, with particular attention to the role of infectious agents and the integration of these observations into everyday clinical practice.

Introduction

A better understanding of the molecular mechanisms of lymphomagenesis is fundamental as it may lead to the development of nonchemotherapeutic agents active in specific lymphoma subtypes, as highlighted in three of the articles included in this CCR Focus section (1–3). Furthermore, infectious agents can represent additional therapeutic targets for lymphoma treatment toward chemotherapy-free therapeutic approaches. While Tsukasaki and Tobinai (4) have reviewed the published data on HTLV-1–associated adult T-cell leukemia–lymphoma, here we summarize the data available on the role of infectious agents in the pathogenesis of marginal zone B-cell lymphomas (MZL). The latter comprise three different entities, namely extranodal MZL of mucosa-associated lymphoid tissue (MALT) type, nodal MZL, and splenic MZL (5). While splenic and nodal MZL are quite rare, each comprising less than 2% of lymphomas, extranodal MZL of MALT type is relatively common, representing around 8% of the total number of non–Hodgkin lymphoma cases.

The term “mantle cell lymphoma” is due to the fact that extranodal MZL, nodal MZL, and splenic MZL are believed to derive from B cells normally present in the marginal zone, which is the outer part of the mantle zone of B-cell follicles. MALT lymphoma is composed of morphologically heterogeneous small B cells, including marginal zone (centrocyte-like) cells, monocytoid cells, small lymphocytes, and scattered (immunoblast- and centroblast-like) large cells; there is a variable degree of plasma cell differentiation. The lymphoma infiltrates the marginal zone of reactive B-cell follicles and extends into the interfollicular region. In epithelial tissues, the neoplastic cells typically penetrate in the epithelium forming lymphoepithelial lesions (6).

The B cells resident in the marginal zone function as innate-like lymphocytes that mount rapid antibody responses to both T-cell–dependent and T-cell–independent antigens (7). Most of the marginal zone lymphocytes are B cells that are involved in the T-cell–independent early immune response and express a restricted immunoglobulin (Ig) repertoire. Postgerminal center memory B cells, needed for the T-cell–dependent immune response, are also localized in the marginal zone. MALT lymphoma presents somatically mutated immunoglobulin heavy chain variable (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 (8, 9). 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 (8). A specific usage of different restricted IGHV families appears to be associated with different anatomic sites or with particular clinical and genetic features (10).

Association of Chronic Inflammation and Infectious Agents with MZL at Various Anatomical Sites

Extranodal MZL occurs most often in organs usually devoid of lymphocytes, where as a result of chronic lymphoid reactive proliferations, the outgrowth of a pathologic clone progressively replaces the normal lymphoid population, giving rise to a MALT lymphoma (11, 12). Autoimmune disorders are, in this context, considered a potential risk factor for development of lymphomas, with, for example, up to an 18.8-fold increased incidence of lymphoma in patients with Sjögren syndrome (13). Also, the antibodies expressed by MALT lymphoma cells generally present specificity for self-antigens (14–16). However, the mechanisms might be distinct in each autoimmune disease. In the case of 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/CD40L (CD40 ligand) and Bcl-2 family proteins, together with the overexpression of B-cell–activating factor (RAFF), may lead to excessive autoantibody production and reduced apoptosis, providing a stimulus for sustained proliferation of B cells (17, 18).

Helicobacter pylori was identified as an etiologic factor in gastric MALT lymphomas following the demonstration, in the early 1990s, of tumor regressions in early-stage cases treated with anti-Helicobacter antibiotic therapy. On the basis of this finding, this tumor became a popular model of the pathogenetic link between chronic inflammation and lymphoma development. Recognition of the driving source of the antigenic stimulation in different tissues may therefore have far-reaching therapeutic implications. Indeed, other bacterial infections have since been found to be implicated in the pathogenesis of MZL arising in the skin (Borreliaburgdorferi; ref. 19), in the ocular adnexa (Chlamyphila psittaci; ref. 20), in the small intestine (Campylobacter jejuni; ref. 21), and possibly in the lung (Achromobacter xylosoxidans; ref. 22). An increased risk to develop MZL has also been reported in patients with chronic hepatitis C virus (HCV) infection (23). The strength of these associations shows, however, vast and not entirely explicable geographic discrepancies.

Genetic Abnormalities in MZL

The genetic relationship among the three MZL subtypes (nodal, extranodal, and splenic) is still unclear. A comprehensive analysis of genomic DNA copy number changes in a very large series of 218 patients with MZL showed that the three MZL types share recurrent trisomies of chromosome 3 and 18 and deletions at 6q23 (TNFα-induced protein 3, TNFAIP3). MALT lymphoma presents significantly more frequently gains at 3p, 6p, 18p, and the del(6q23) (24). Splenic MZL, instead, is associated with del(7q31) and del(8p) (24, 25). Nodal MZL does not show statistically significant differences compared with MALT lymphoma and lacks the splenic MZL-related 7q losses (24). Differently from the other two MZL types, MALT lymphoma presents recurrent chromosomal translocations (Table 1; refs. 26–33), and at least three of them (BIRC3–MALT1, IGHV–BCL10, IGHV–MALT1) lead to activation of the NF-κB pathway. The latter is also constitutively activated following the inactivation of TNFAIP3 by either somatic mutation or del(6q23), which represents a common genetic aberration across all MZL subtypes (24, 34). In splenic and nodal MZL, additional members of the NF-κB pathway, including BIRC3, are deregulated by genetic lesions, which are mutually exclusive to those activating the NOTCH pathway (35–40). Differently from NF-κB deregulation, genetic lesions activating the NOTCH pathway, mostly represented by somatic mutations in the NOTCH2 gene, have so far not been reported as common events in MALT lymphomas (36, 40, 41).

### Table 1. Most common chromosomal translocations detected in MALT lymphomas

<table>
<thead>
<tr>
<th>Genetic lesion</th>
<th>t(11;18)(q21;q21)</th>
<th>t(14;18)(q32;q21)</th>
<th>t(1;14)(p22;q32)</th>
<th>t(3;14)(p13;q32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved genes</td>
<td><strong>BIRC3–MALT1</strong></td>
<td><strong>IGHV–MALT1</strong></td>
<td><strong>IGHV–BCL10</strong></td>
<td><strong>IGHV–FOXP1</strong></td>
</tr>
<tr>
<td>NF-κB activation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Frequency</td>
<td>15%–40%</td>
<td>20%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Preferential sites</td>
<td>Stomach, lung</td>
<td>Lung, salivary gland, skin, ocular adnexa</td>
<td>Stomach, lung</td>
<td>Unclear</td>
</tr>
<tr>
<td>Clinical relevance</td>
<td>Antibiotic resistance</td>
<td>Antibiotic resistance?</td>
<td>Antibiotic resistance</td>
<td>Transformation risk?</td>
</tr>
</tbody>
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Alkylating agents resistance?
Of clinical relevance, although MALT lymphomas bearing the t(11;18) present a lower risk of transformation to diffuse large B-cell lymphoma (DLBCL; ref. 42), they have a low probability of response to antibiotics, are more commonly H. pylori–negative, and are associated with more advanced disease (43–45). Also, the t(3;14) has been more commonly associated with a low probability of response to antibiotics, are more commonly H. pylori–negative, and are associated with more advanced disease (43–45). Also, the t(3;14) has been associated with a risk of transformation to high-grade tumors (46, 47).

The H. pylori and Gastric MALT Lymphoma Pathogenetic Model

Initially, H. pylori infection was demonstrated in the gastric mucosa of more than 90% of gastric MALT lymphoma cases (48) and a pivotal case–control study showed an association between previous H. pylori infection and the development of primary gastric lymphoma (49).

Subsequent studies showed a comparatively lower incidence (50, 51). Interestingly, a population-based study from northern Italy showed a declining incidence of H. pylori–associated gastric MALT lymphomas in the past decade: This appears most likely due to a decreasing prevalence of the infection in recent cohorts and to a changed management policy, which now favors an early generalized treatment with proton pump inhibitors in patients with acid peptic disease symptoms, without a diagnostic gastroscopy (52).

More 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 (11, 51) and from a series of in vitro studies showing that gastric MALT lymphoma cell growth could be stimulated in culture by H. pylori strain–specific T cells (53). Additional studies have suggested an oncogenic property for the H. pylori cytotoxin–associated gene A (CagA) protein. CagA would enter B cells, bind, and activate SHP-2, leading to ERK and MAPK activation and upregulation of the antiapoptotic molecules BCL2 and BCXL (54). Finally, following the initial study by Wotherspoon and colleagues (55), several groups have confirmed that eradication of H. pylori organisms with antibiotics and proton pump inhibitors results in regression of gastric MALT lymphoma in more than 75% of cases (Table 2; refs. 12, 56, 57).

As reviewed elsewhere (10, 58), the immune cells in the tumor microenvironment play a relevant role in gastric MALT lymphomagenesis. In vitro experiments have demonstrated that the growth and differentiation of MALT lymphoma cells are partially dependent on H. pylori–specific intratumoral T cells stimulated by H. pylori antigens and that B-cell proliferation requires CD40/CD40L-mediated signaling and Th2-type cytokines (53, 59–61).

Lymphoma proliferation can also be enhanced by a CD40/CD40L-independent mechanism that involves the recruitment of CD4+CD25+FOXP3+ regulatory T cells (Treg) through the secretion of specific chemokines such as CCL17 and CCL22 by B cells (62). In vivo studies examined the influence of Tregs on the lymphoma response to anti-Helicobacter treatment, showing that a higher number of tumor-infiltrating FOXP3+ Tregs at baseline is significantly associated with lymphoma sensitivity to antibiotic treatments and its H. pylori dependence (63, 64).

Effective communication between B cells and T cells depends on the interactions between costimulatory molecules of neoplastic B cells (such as CD80 and CD86) and T-cell receptors (CD28 and CTLA-4; ref. 61). Interestingly, CD86 expression was found to be significantly associated with the responsiveness to eradication of H. pylori (65). The T-cell dependence of MALT lymphoma cells may be an explanation for the long-term tendency of most gastric MALT lymphomas to remain localized.

In addition to the above-mentioned T-cell indirect role, the growth of MALT lymphoma tumors can also be initiated

![Table 2. Lymphoma regressions after anti-infectious treatment in different types of MZL at different sites](image)

<table>
<thead>
<tr>
<th>Involved organ</th>
<th>Targeted pathogen</th>
<th>Antibiotic regimen</th>
<th>Type of study</th>
<th>Patients (n)</th>
<th>Overall lymphoma remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>H. pylori</td>
<td>Mostly proton pump inhibitor plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days</td>
<td>&gt;30 studies either retrospective or prospective</td>
<td>&gt;1,400</td>
<td>~75%</td>
</tr>
<tr>
<td>Ocular adnexa</td>
<td>C. psittaci</td>
<td>Doxycycline, 100 mg twice a day × 21 days</td>
<td>2 prospective, 4 retrospective, 1 case report</td>
<td>120</td>
<td>48%</td>
</tr>
<tr>
<td>Skin</td>
<td>B. burgdorferi</td>
<td>Ceftriaxone, 2 g/day × 14 days (in most cases)</td>
<td>Case reports</td>
<td>5</td>
<td>40%</td>
</tr>
<tr>
<td>Various (also including nodal and splenic MZL)</td>
<td>HCV</td>
<td>IFN plus ribavirin</td>
<td>7 retrospective series and several case reports</td>
<td>&gt;110</td>
<td>~75%</td>
</tr>
</tbody>
</table>
by self-antigen–triggered B-cell receptor (BCR) signaling (14). Several studies have suggested a relevant role for chemokine receptor–mediated signaling (10, 58, 66). CXC1L3 (BCA-1) and its chemokine receptor CXCR5 are highly expressed and regulate the B-cell homing in H. pylori–positive gastric MZL (66). Upregulation of CCR7, CXCR3, CXCR7, and CXCL12 as well as downregulation of CXCR4 are features of most extranodal MZL (10, 58). In H. pylori–associated gastric lymphomas, high CXCR3 expression seems to be associated with tumor progression and escape from H. pylori dependence (58).

H. pylori strains expressing the CagA protein seem to induce more severe gastritis or peptic ulcerations and have been associated with the development of gastric adenocarcinoma (67). Anti-CagA antibodies can be detected in most cases of MALT lymphomas at a significantly higher rate than in active gastritis, indicating that CagA-positive H. pylori strains may also be linked with the development of gastric MALT lymphoma (67). CagA strains of H. pylori have been associated with a more frequent presence of the t(11;18) (q21;q21) in gastric MZL (32). CagA-positive strains of H. pylori are much more potent in inducing host inflammatory responses, including the activation of neutrophils, which release highly genotoxic reactive oxygen species. Interestingly, neutrophil infiltration is more prominent in H. pylori–associated gastritis than in MALT at other sites, suggesting that oxidative damage might play a role in the development of t(11;18) (q21;q21) and other B-cell genetic alterations that may favor the growth and progression of gastric MZL (32). This hypothesis is supported by data from Rollinson and colleagues, who showed that interindividual differences in antioxidative capacity and in the cellular inflammatory responses to H. pylori infection may represent the genetic background of H. pylori–associated lymphoma genesis (68).

All the findings summarized above are in keeping with a possible model (Fig. 1) of multistage development and progression from chronic gastritis to gastric lymphoma that would start with H. pylori infection, stimulating the formation of a lymphocytic infiltration in the gastric mucosa. As a result of an antigenic stimulation (autoantigen and T cells specific for H. pylori) combined with direct effects on the B cells, the latter would proliferate and might sporadically undergo a neoplastic transformation following the acquisition of genetic abnormalities, perhaps facilitated by the presence of free radicals (32, 68). The accumulation of genetic abnormalities would be associated with both a loss of dependency of antigenic stimulation (with subsequent antibiotic resistance) as well as a possible histologic transformation (69). Regarding the last point, it should be mentioned that pathologic lymphoma remission after first-line H. pylori eradication therapy has been reported also in some patients with H. pylori–positive early-stage DLBCL of the stomach with or without concomitant or prior histologic evidence of MALT lymphoma (70, 71). This finding suggests that the loss of antigen dependence and high-grade transformation may be separate events in the progression of gastric lymphoma.

C. psittaci and Ocular Adnexal MZL

C. psittaci is the second most thoroughly studied among the bacteria reported to have a potential pathogenetic role in MZL. The Chlamydia psittaci genus is the etiologic agent of psittacosis, an infection caused by exposure to infected animals, which is a rare condition in the European population. The presence of C. psittaci DNA has been detected in a variable percentage of MZL, mainly of the ocular adnexa (i.e., conjunctiva, lacrimal gland, orbital fat, eyelid, or lacrimal sac), but also in MZL of the lungs, skin, thyroid gland, and salivary glands (72, 73). However, the prevalence of C. psittaci infection in ocular adnexal lymphomas 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 (74, 75).

A great deal of evidence supports a pathogenetic association between C. psittaci and the development of MALT lymphoma of the ocular adnexa, ranging from the identification of chlamydial antigens in tumor tissue by immunohistochemistry and the detection of bacterial DNA in the tumor biopsies, to the visualization of the bacteria within tumor-infiltrating macrophages by electronic microscopy and their isolation from conjunctival swabs and the peripheral blood of patients (76, 77). Moreover, development of metachronous C. psittaci–related lymphomas was described in the same patient after prolonged exposure to an infected animal (78). The finding that C. psittaci infection has been detected in up to approximately 80% of Italian patients with ocular adnexa MALT lymphoma provided the rationale for the antibiotic treatment of localized lesions (20, 75). Moreover, the eradication of C. psittaci infection with doxycycline for patients with ocular adnexa MALT lymphoma resulted in lymphoma regression in approximately 50% of patients (Table 2), even in those with multiple treatment failures, previously irradiated lesions, or regional lymph node involvement (79, 80). As in the case of H. pylori, the observed lymphoma regressions following eradication of C. psittaci suggest a pathogenetic role of the infection.

Of note, MZL regression after doxycycline treatment has also been observed in some lymphomas with no C. psittaci presence as well as in cases in which this treatment failed to eradicate the C. psittaci infection (76, 80, 81). This finding suggests that other doxycycline-sensitive microorganisms may be linked with the lymphoma.

B. burgdorferi in Cutaneous MZL

B. burgdorferi, an Ixodes tick-borne spirochete, is implicated in different dermatologic conditions (erythema migrans, lymphadenosis benigna cutis, and acrodermatitis chronica atrophicans) possibly associated with lymphoproliferative skin disorders. However, the historical literature is confusing, often lacking unequivocal criteria for the pathologic identification and classification of cutaneous pseudolymphomas and lymphomas (19).

The prevalence of Borrelia infection in patients with cutaneous MZL exhibits important variations among
different geographic areas, with higher detection rates in endemic areas. In Europe, DNA of *B. burgdorferi* has been detected in 10% to 42% of patients with cutaneous MZL (82). Anecdotal case reports document a histologic regression of cutaneous MZL after *B. burgdorferi* eradication (Table 2), thus corroborating the hypothesis that a chronic *B. burgdorferi* infection could represent the background for the development of cutaneous MZL (83). Indeed, there are several homologies between *H. pylori* and *B. burgdorferi* infections (19). Both microorganisms can generally be localized in extracellular sites and in both infections a specific T-cell immune response plays a role. Moreover, both infections can persist in the host despite active local and systemic immune responses and both induce the development of an acquired lymphoid tissue in organs where it is normally absent.

**Immunoproliferative Small Intestinal Disease and *C. jejuni***

Immunosuppressive small intestinal disease (IPSID), previously also known as α-heavy chain disease or Mediterranean lymphoma, is a special subtype of MALT lymphoma (6, 84, 85). Although it is endemic in the Middle East, especially in the Mediterranean area, IPSID can also be diagnosed in industrialized Western countries, usually among immigrants from the endemic area. The production of α-heavy chain, the most typical feature of IPSID, is...
present in up to 75% of cases, while, in the remaining cases, \( \alpha \)-heavy chain is not secreted but it is still demonstrable by immunohistochemistry.

In its early, potentially reversible phases, IPSID can be managed with sustained 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. If left untreated, however, the lymphoma can undergo a histologic transformation into a DLBCL. These results suggest a role for an infectious agent, and \( C. \) jejuni is, so far, the best candidate (21). Unlike the case for other bacterial infections, the level of evidence supporting a pathogenetic link of \( C. \) jejuni with IPSID is, however, very weak. A single study (21) followed by a confirmatory case report (82) described lymphoma improvement in 1 patient treated with antibiotics directed against \( C. \) jejuni and the presence of \( C. \) jejuni DNA in 5 of 7 archival cases.

In contrast with other infectious agents that have been associated with lymphoma, \( C. \) jejuni is an unlikely cause of cancer. Indeed, this microorganism is not known to be a persistent colonizer of humans. Within 2 weeks after acute infection, \( C. \) jejuni is usually no longer detectable in the stool. However, recurrent asymptomatic infections may be frequent in the developing countries where IPSID is endemic; yet, these infections are thought to be transient (86).

**A. xylooxidans and Pulmonary MALT Lymphoma**

\( A. \) xylooxidans is a gram-negative betaproteobacterium 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.

Preliminary data have shown a possible link between pulmonary MALT lymphoma and this microorganism, detecting it in 12 of 25 examined cases (87). These cases were included in a larger series of 124 pulmonary MALT lymphomas and 82 control tissues from six European countries (22). This study showed a significantly increased prevalence of \( A. \) xylooxidans infection in MALT lymphomas (46%) than in nonlymphoma lung biopsies (18%) but with marked geographical variations of the infection prevalence in patients with lymphoma (ranging from 67% in Italy to 33% in the United Kingdom; ref. 22). Further studies are warranted to investigate the potential pathogenic role of the microorganism as no data demonstrating a causal relationship has yet been provided.

**Hepatitis C Virus and MZLs**

Hepatitis C virus is an enveloped, positive-stranded RNA virus of the Flaviviridae family; it comprises at least six major genotypes, whose prevalence varies among different countries. HCV is not only hepatotropic, but also lymphotropic as it infects both hepatocytes and lymphocytes. Numerous epidemiologic, clinical, and biologic data have suggested an association between HCV infection and the pathogenesis of at least a portion of B-cell non-Hodgkin lymphoma. The biologic basis of this relationship has not been completely clarified (88, 89). HCV directly infects and replicates inside hepatocytes (90), but does not integrate into the host genome and does not contain an obvious oncogene (88).

Yet, a true replication in lymphocytes has not been fully demonstrated. Analogous to observations in MZL associated with bacterial infections, restricted combinations of the IGHV gene repertoire have been found in HCV-associated MZL (88, 91).

Several potential pathogenic mechanisms have been proposed to explain a causative link with the lymphoma growth: a nondirect antigen-driven stimulation, a direct oncogenic role of HCV, a viral immunosuppressive effect on the tumor cells, and coinfection by another unknown oncogenic virus. Although these different putative mechanisms of HCV-induced lymphomagenesis do not have to be mutually exclusive, they remain largely hypothetical (88).

Significant data comes from epidemiologic studies showing a high prevalence of HCV seropositivity in patients with B-cell non-Hodgkin lymphoma (92–96). There are, however, important geographical variations in the prevalence of chronic HCV infection worldwide, with the highest prevalence (>10%) in Egypt, central Africa, Mongolia, and Bolivia (97). Thus, the prevalence of HCV-associated lymphomas is also extremely variable among different countries. Two systematic reviews of more than 60 studies have indicated that, overall, 13% to 18% of B-cell lymphomas are associated with HCV infection (94, 96), and globally the relative risk of being infected is approximately two to four times higher among patients with B-cell lymphoma than in the general population. MZL, in particular splenic and nodal MZL, but also extranodal MZL (mainly at nongastric sites), are the lymphoma subtypes most frequently described as being HCV related (91, 98–100). However, high prevalence of DLBCL and lymphoplasmacytic lymphoma has also been reported.

The clinical features of HCV-associated lymphoma, at least in some reports, appear to be peculiar. This may partly depend on the presence of HCV infection. This kind of lymphoma often arises in target organs of HCV, such as the spleen, liver, and the salivary glands (101). More frequently than in HCV-negative cases, there are increased transaminase levels, monoclonal gammopathies, autoimmune phenomena, rheumatoid factor, and asymptomatic cryoglobulinemia (102). Indeed, type II mixed cryoglobulinemia can often precede the development of HCV-associated B-cell lymphomas (23, 88).

The strongest evidence for a causal relationship between HCV and lymphoma came from the first observation of lymphoma regression in 9 patients after antiviral treatment with IFN\( \alpha \) and ribavirin (103). Additional studies confirmed that the achievement of a virologic response is followed by a MZL remission in about 75% of the cases (Table 2; refs. 23, 104). Hence, the presence of HCV may have clinical consequences, and mandatory initial staging of MZL should include serology for HCV (105). It seems advisable to consider antiviral treatment with pegylated IFN\( \alpha \) and ribavirin as first-line therapy in patients with
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