Clinical Presentation and Management of Marginal Zone Lymphomas

Catherine Thieblemont

Marginal-zone lymphoma (MZL) includes three subtypes depending on the site of lymphoma involvement: extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma); splenic MZL; and nodal MZL. Beside a common cell-of-origin and similarities concerning a possible chronic antigenic stimulation by microbial pathogens and/or autoantigens, the clinical presentation is very different with symptoms related to lymphoma location. MALT and splenic MZL present with an indolent disease with good performance status, no B symptoms, and no adverse prognostic factors and are associated with long survival. Patients with nodal MZL present with a more aggressive disease and have a shorter failure-free survival. Clinical and biological prognostic factors identified in reported series are heterogeneous. The optimal treatment has yet to be defined for the three subtypes, and current strategies will be described in this review.

Marginal zone B-cell lymphomas (MZL) represent a group of lymphomas whose cells originate from B lymphocytes normally present in a distinct anatomical location, the so-called "marginal zone" (MZ) of the secondary lymphoid follicles.[1] These cells are anatomically localized in the lymphoid organs (spleen and lymph nodes) and in the non-lymphoid organs (mucosa-associated lymphoid tissue [MALT] or non-mucosal tissue such as skin, orbit and dura). Depending on the site of involvement, the International Lymphoma Study Group individualized three distinct subtypes of MZL: (1) extranodal MZL of MALT type, (2) splenic MZL (with or without villous lymphocytes), and (3) nodal MZL (with or without monocytoid B cells).[2,3] Despite this classification, the relative rarity of these lymphomas and difficulties in distinguishing them from other low-grade lymphoma subtypes are obstacles to conducting epidemiological surveys and to describing clinical features and outcomes. Moreover, no prospective studies on large series have been published to date, making therapeutic decisions difficult. Data regarding clinical and biological prognostic markers are limited, and it is therefore difficult to predict those in whom the disease will be more aggressive. This review will present recent data describing the epidemiology, clinical features, staging, and therapy of these lymphomas.

Correspondence: Catherine Thieblemont, MD, PhD, Centre Hospitalier Lyon-Sud, Pavillon 1F, Pierre-Benite 69310, France; Phone: +33 (0)4 78864305, Fax: +33 (0)4 78864354, catherine.thieblemont@chu-lyon.fr

Acknowledgements: The author thanks Bertrand Coiffier, Pascale Felman, Françoise Berger, Evelyne Callet-Bauchu, Alexandra Traverse-Glehen, Lucile Baseggio, Sophie Gazzo, and Martine Ffrench for their input and assistance.

Epidemiology

MZL account for between 5% and 17% of all non-Hodgkin lymphomas (NHL) in adults depending on the series. MALT lymphoma is the most frequent of the MZL subtypes, representing 50% to 70% of MZL and 7% to 8% of NHL. The splenic and the nodal MZL represent 20% and 10% of MZL, respectively, and account for less than 1% of NHL. Most of the cases occur in adults, with a median age of approximately 60 years, except for splenic MZL with villous lymphocytes (SLVL), occurring in adults at a median age of around 70 years.[4-8]

Growing evidence indicates that MZL of MALT, splenic and nodal types are associated with chronic antigenic stimulation by autoantigens and/or microbial pathogens, inducing an accumulation of lymphoid tissue in the typical sites of involvement for each lymphoma entity in mucosa or organs that contain no native lymphoid tissue for MALT lymphomas, in spleen for splenic MZL, and in nodes for nodal MZL. In the case of autoimmunity, several diseases have been associated with an increase risk of MALT lymphoma, such as Hashimoto thyroiditis, myoepithelial sialoadenitis (MESA) with or without associated Sjögren syndrome, or lymphoid interstitial pneumopathy. Based on epidemiological studies, molecular investigations, and therapeutic success of lymphoma regression with antibiotics, five distinct microbial pathogens have now been identified to be related to MZL. *Helicobacter pylori* is the best characterized and is associated with gastric MALT lymphoma.[9] Other chronic infections have been described in cases of MZL, although their role in pathogenesis remains to be firmly established. *Borrelia burgdorferi* associated with Lyme disease has been proposed to play a possible role in cutaneous MALT lymphoma.[10] *Campylobacter jejuni* in small intestine has been associated with immunoproliferative small intestinal disease (IPSID),[11] *Chlamydia psittaci* infection with ocular adnexal MALT lymphoma,[12]

and hepatitis C virus (HCV) infection with MALT, splenic and nodal MZL.[13,14] Identification of such microbial antigens that may play a pathogenic role in lymphomagenesis through chronic stimulation and indirect transformation of lymphoid cells has important therapeutic implications for these diseases.

MALT Lymphomas

Clinical features of MALT lymphomas

The clinical presentation of MALT lymphomas varies according to the lymphoma location (**Table 1**; **Figure 1**; see Color Figures, page 549), but shared characteristics can be described. Most MALT lymphoma patients present at diagnosis with an indolent disease with good performance status (PS), absence of B symptoms, and no adverse biological prognostic factors such as high lactate dehydrogenase (LDH) or β2-microglobulin levels.[13,15,16] Disease is localized for the majority of the patients but multifocal lesions are present in 30% to 40% of patients.[17] Dissemination of the disease occurs either to other mucosal sites or, more often, by extension from a mucosal site to a non-mucosal site such as spleen, bone marrow, or liver. Bone marrow involvement is detected in 20% of the cases. Risk of dissemination is significantly higher for non-gastrointestinal (GI) tract lymphomas.[17]

Staging

The staging procedures in MALT lymphomas are not standardized, particularly with regard to the number of the extranodal sites that need evaluation at diagnosis. Early dissemination of the disease occurs in nearly 35% of the patients without changing their outcome.[17] Therefore, pretherapeutic procedures including extensive staging in patients to meticulously assess dissemination is probably not necessary. Guidelines concerning this staging are reported in **Table 2**. The second difficulty in staging MALT lymphoma is the application of the traditional staging systems for nodal-type lymphoma to MALT-type lymphoma. The Ann Arbor system is based on the extension from contiguous nodes and can be misleading in MALT-type lymphomas, since the involvement of multiple extranodal sites, particularly within the same organ (e.g., skin, gastric), may not reflect truly disseminated disease. The gastric issue has been particularly discussed in several international meetings and alternative staging systems have been proposed.[18]

Treatment

Despite abundant literature on pathophysiological features of MALT lymphomas, only few retrospective series of surgery, irradiation or chemotherapy are reported. The International Extranodal Lymphoma Study Group (IELSG) has an ongoing effort to coordinate studies in these diseases.[19]

The unique pathogenesis of MZL related to possible microbial pathogens that may initiate the disease has an impact on therapy. For localized disease, there is increas-

Table 1. Clinical features of MALT lymphoma considering the most frequent sites of lymphoma involvement[15-17,43-45]

	Gastrointestinal Tract Location		Non-gastrointestinal Tract Location					
	Stomach	Intestine	Lung	Thyroid	Head and Neck (Salivary glands)	Skin	Orbit	Breast
Age, median, years	56	59	60	60	63	55	63	55
Male: female ratio	1:1.7	1.2:1	1:1.7	0:10	1:4.5	1.1:1	1:2	1:1.5
Localized disease	87%	45%	62%	83%	73%	59%	67%	40%
Bone marrow involvement	13%	35%	38%	17%	18%	29%	10%-22%	20%
Symptoms at presentation								
B symptoms								
Weight loss	15%-32%	50%	10%-19%	0-7%	7%	–		0%
Fever and night sweat	3.5%, range 1%–9%	–	–	0-7%	7%	24%		0%
Specific to location	Epigastric pain 53-81%	Abdominal pain	Asymptomatic 56%	Thyroid 100%	Asymptomatic 95%	Nodule	Orbital mass	Breast mass
	Dyspepsia 32-34%	Occlusion	Cough 17%	Mass 9-23%	Mass 5%	Erythema	Bulging eye	Breast pain
	Vomiting 8-31%	Perforation	Dyspnea 15%	Hoarseness 30%	Auditory trouble	Pruritus	Diplopia	
	Gastric bleeding 2-33%		Hemoptysis 7%	Dysphagia 30%				
	Anemia (Hb < 12g/L) 30%		Chest pain 2%	Dyspnea				

Abbreviations: –, no data

Table 2. Recommended staging procedures for MALT lymphoma.

- History
- Complete physical examination
- Imaging
  - Computed tomography scan of thorax, abdomen and pelvis
- Laboratory tests
  - Blood count (with peripheral blood smear)
  - LDH level
  - β2-microglobulin level
  - Serum electrophoresis and immunoelectrophoresis with immunofixation
  - Renal and liver functions
  - HIV serology
  - HCV serology
  - optional: albumin level
- Bone marrow biopsy
- Depending on the symptoms at diagnosis:
  - gastrointestinal tract locations
    - Gastric location: endoscopy and echoendoscopy; *Helicobacter pylori*: systematic histologic examination
    - Intestinal location: colonoscopy; +/- double-contrast X-ray of the small bowel; if small intestine *Campylobacter jejuni*: PCR in lymphoma biopsy; in situ hybridization and/or immunohistochemistry
  - non-gastrointestinal tract locations
    - Lung: endoscopy + lavage
    - Head and neck (salivary gland, tonsils, parotid): otolaryngologic investigation and echography
    - Thyroid: neck echography +/- CT scan and functional thyroid tests
    - Orbit (ocular adnexa): NMR and ophthalmologic examination; *Chlamydia psittaci*: PCR on lymphoma biopsy and peripheral blood mononuclear cells
    - Skin: *Borrelia burgdorferi:* PCR in lymphoma biopsy
    - Breast: computed tomography scan

Depending on the treatment proposed to the patient:
- Echocardiography
- Sperm conservation

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; NMR, nuclear magnetic resonance

ing evidence indicating that antibiotics can be effectively employed as the sole initial treatment. In the stomach, eradication of *H pylori* leads to complete regression of the lymphoma in nearly 80% of the cases.[20] In ocular adnexal, skin, and small intestinal MALT lymphomas, an objective clinical response has been observed in some patients after antimicrobial treatment.[11,12,21] However it is still unknown whether eradication of microorganisms will definitively cure the lymphoma. In gastric MALT lymphoma, polymerase chain reaction (PCR)-detectable B-cell monoclonality may persist after the disappearance of histological evidence of MALT lymphoma, suggesting that *H pylori* eradication suppresses but does not eradicate the lymphoma clone.[22]

There are no treatment guidelines for the management of patients with MALT lymphoma associated with microbial pathogens who fail antibiotic treatment, or for those with MALT lymphoma not associated with microbial pathogens. For localized disease, local treatment (either radiotherapy or surgery) will usually achieve excellent disease control.[23,24] In patients with disseminated disease at presentation, single agents such as alkylating agents (cyclophosphamide or chlorambucil) or fludarabine have been reported to induce a 75% complete remission rate, with projected 5-year event-free and overall survival rates at 50% and 75%, respectively.[25] Anthracyline-based chemotherapy has to be reserved for patients with histological transformation or with high tumor mass (i.e., high LDH, mass greater than 7 cm). Recently rituximab has been reported to induce an overall response rate of around 75%, with better results as first-line therapy,[19,26] and may have a real place in the management of MALT lymphoma. An ongoing international trial is currently testing whether the combination of rituximab with chlorambucil enhances the activity of chlorambucil (IELSG19). The treatment of these patients, until the conclusion of prospective trials, is summarized in **Figure 2**.

Outcome and Prognostic Factors

Patients with MALT lymphoma have a favorable outcome with 5-year overall survival reported between 95% and 86% (**Figure 3**; see Color Figures, page 549), without any significant difference between GI or non-GI lymphoma and between localized and disseminated disease.[13,16,17] Median time-to-progression is estimated at around 5 years (**Figure 3**; see Color Figures, page 549) and is significantly higher for the GI locations compared to the non-GI locations (8.9 versus 4.9 years, respectively; $P = .01$).[17] Recurrences may involve different extra-nodal sites or nodal sites. Histologic transformation to large cell lymphoma is reported to occur in less than 10% of the cases, usually late in the course of the disease and independent of dissemination.[13]

Prognosis in MALT lymphoma has been reported to be influenced by prognostic factors for lymphoma including poor PS, bulky tumor, and high levels of LDH, β2-microglobulin, and serum albumin.[16,27] The presence of a large-cell component at diagnosis is also associated with a poorer outcome.[16,27] Influence of systemic dissemination on survival is controversial, being significantly associated with poorer prognosis in some studies.[17,28] Interestingly the t(11;18)(q21;q21), a translocation specific of MALT-type lymphoma and detected in 18% to 24% of patients with gastric MALT lymphoma, has been correlated to a resistance to *H pylori* eradication therapy[29] and to alkylating agents[30] and but not to rituximab.[26]

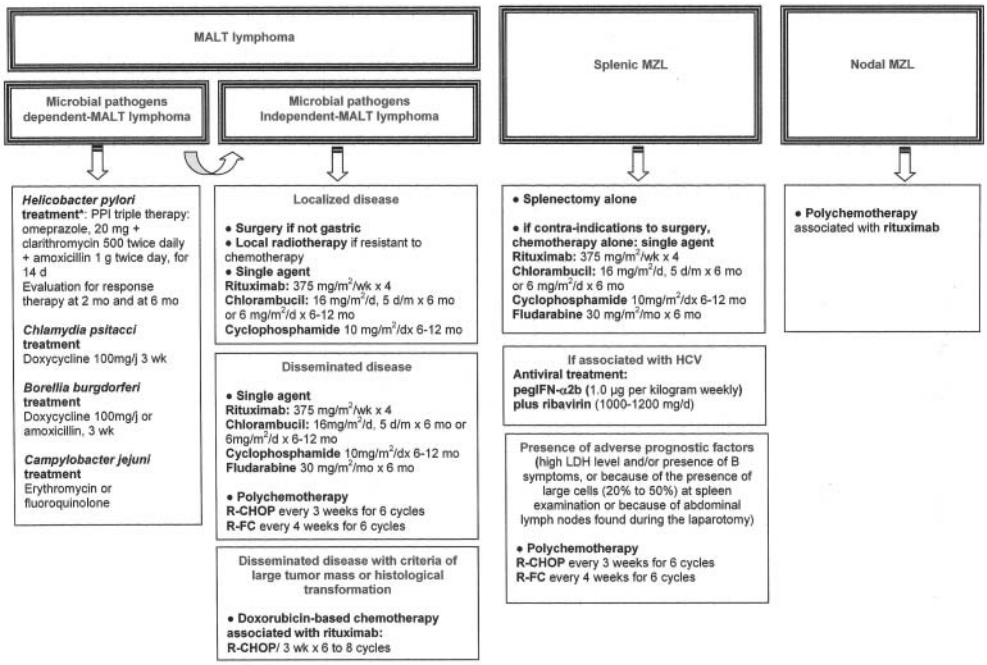

Figure 2. Suggestions for treatment of patients with marginal zone B-cell lymphoma (MZL).

Abbreviations: HCV, hepatitis C virus; IFN, interferon; LDH, lactate dehydrogenase; R-CHOP, rituximab, vincristine, doxorubicin, cyclophosphamide, predisolone; R-FC, rituximab, fludarabine, cyclophosphamide

Splenic MZL

Clinical features of splenic MZL

Splenic MZL is rare and overlaps with other indolent lymphomas. The hallmark of the clinical presentation is usually splenomegaly.[4,5,31] The splenomegaly becomes symptomatic when massive and/or associated with cytopenias. Early in the disease, however, the splenomegaly may be detectable only on computed tomography (CT) scanning. Small involved splenic hilar lymph nodes are frequently present. Peripheral lymph node involvement is unusual;[3] if it is present, the presentation is usually classified as a disseminated nodal and splenic subtype.[6]

Bone marrow and blood involvement are present in 95% of patients with splenic MZL.[31] In 15% of the cases, blood involvement is represented by villous lymphocytes, lymphocytes displaying cytoplasmic protrusions.[31] It is controversial whether splenic lymphoma with villous lymphocytes (SLVL) is the leukemic counterpart of all splenic MZL or whether it is a subentity of splenic MZL. It is presently agreed that the SLVL applies to patients with more than 20% villous lymphocytes in the blood. Whereas the serum LDH level is usually normal in splenic MZL, the β2-microglobulin level is increased. A large proportion of patients have a serum monoclonal paraprotein (M-component), mainly of the µ (IgM) isotype.[31]

In some patients, the first manifestation of the lymphoma is an immune hemolytic anemia or an immune thrombocytopenia. These patients may respond to corticosteroids. Uncommonly, autoantibodies against coagulation factors are present.

Splenic MZL associated with HCV infection has been described, particularly in northern Italy.[32] HCV-associated splenic MZL are indistinguishable from classic splenic MZL, except for the presence of HCV viral replication and coexistence of a liver disease.[33]

Diagnostic procedures and positive diagnosis

Patients with splenic MZL often present with lymphocytosis, cytopenias, or symptomatic splenomegaly. Bone marrow examination shows an involvement in 90% of the cases. The morphology and immunophenotype of these cells usually suggest the diagnosis of splenic MZL. The presence of characteristic cytogenetic abnormalities such as 7q deletion may confirm this. When the blood and bone marrow are not involved, the diagnosis can only be made after splenectomy.

Treatment

Patients with moderate asymptomatic splenomegaly may be followed without any treatment.[4,5,31,34] The absence of treatment does not influence the course of the disease and these patients often have stable disease for at least 10 years.[5,35]

When treatment is indicated (i.e., occurrence of a large symptomatic splenomegaly and/or cytopenia), splenectomy is the treatment of choice.[31] Splenectomy is beneficial in terms of improvement of performance status and correction of cytopenias[4,31] This benefit, which is due to the disappearance of hypersplenism but also the reduction of mar-

row infiltration after splenectomy,[36] persists for years, with an interval before requiring further treatment of over 5 years, even if the patient develops progressive lymphocytosis.[31]

Chemotherapy based on alkylating agents (chlorambucil or cyclophosphamide) or purine analogues (fludarabine) has also been reported as an effective treatment in non-randomized studies or in retrospective analyses.[31,37] The role of adjuvant chemotherapy in the setting of adverse prognostic factors such as high LDH level and/or presence of B symptoms, or because of the presence of large cells (> 20%) has not been established. Although chemotherapy may increase the number of complete responses, it has no impact on the risk of relapse, histological progression, or survival in comparison to patients who receive no adjuvant chemotherapy.[31] Chemotherapy alone may be proposed initially to patients with contraindications to surgery but who required treatment or later for patients with clinical progression after splenectomy. In this setting, good responses have been reported with single-agent fludarabine but not with 2-deoxycoformycin.[38] Good responses have been observed with rituximab in patients refractory to standard chemotherapy.

In cases of HCV-associated splenic MZL, antiviral treatment with interferon (IFN)-α or IFN-α plus ribavirin has been reported in a small series to be associated with a marked reduction of lymphocytosis and splenomegaly, whereas antiviral therapy is ineffective in HCV-negative splenic MZL.[33] This very interesting observation warrants further follow-up.

Outcome and prognostic factors

Patients with splenic MZL have a long survival in most reported series, with more than 50% survival at 5 years.[4,5,31,34] Progression to lymph nodes or extranodal sites may occur. described with a median time to progression is 3.7 years, with no difference between non-SLVL cases and SLVL patients.[31]

Histological transformation to diffuse large B cell lymphoma (DLBCL) is rare, occurring at time of tumor recurrence in 10% to 20% of patients, and is clinically associated with B symptoms, poor performance status, disseminated disease in nodal and extra-nodal locations, high LDH, and poor outcome (median survival of 26 months[31]). Transformation may occur at diagnosis (seen on the removed spleen) or at time of progression with a median time to transformation of 12 to 85 months.[31,39] Transformation is frequently associated with p53 inactivation or new chromosomal abnormalities.

No specific prognostic factors have been described for splenic MZL, although the International Prognostic Index (IPI) is often used. However, in our experience, none of these criteria (age, PS, stage, number of extranodal sites, and LDH level) influence outcome.[31] Leukocyte count > 30 or > 20 x 10^9/L, lymphocytes < 4 or > 20 x 10^9/L, β2-microglobulin level, presence of monoclonal component, and initial treatment with chemotherapy have been described as adverse prognostic factors.[5,31,34]

Nodal MZL With or Without Monocytoid B-Cells

Clinical presentation

Because of the more recent identification of this lymphoma, clinical data restricted to nodal MZL may be found in only three reports in the literature,[8,14,40] with limited numbers of patients. The median age for these patients is 50 to 62 years, with a slight female predominance. The vast majority of the patients present with disseminated, peripheral and visceral nodal involvement with bone marrow involvement in less than half of the patients (28%, 43%, and 44%, respectively[7,8,14]). There is no difference among these groups with respect to B symptoms, elevated LDH, performance status, or IPI score compared to other primary nodal B-cell lymphomas such as follicular lymphomas.[7] Elevated β2-microglobulin is found in one-third of the patients, and an M-component is infrequently detected (8%).[41] Cytopenias are rare,[14] and few cases are reported to be associated with HCV.[14]

Outcome and prognostic factors

The outcome of patients with nodal MZL is similar to that of patients with splenic MZL but worse than that of patients with MALT lymphoma (**Figure 3**; see Color Figures, page 549). Estimated 5-year overall survival is reported between 50% and 70%,[7,8] without any plateau suggesting that the disease is not currently curable. The estimated median time to progression is between 1 and 2 years.[7,41] This may be explained by the fact that 20% of patients present at diagnosis with a component of large cells (> 20%) and a high mitotic count with evidence for transformation into diffuse large B-cell lymphoma.[7] Given the small numbers of cases reported, no specific prognostic factors are proposed. At the time of relapse, nodal involvement is usually predominant, although splenic or extranodal involvement may occur.

Treatment

A precise recommendation for therapy is difficult because of the limited available data. The disease is characterized as having a good survival but a short time to progression, and logical treatment options include polychemotherapy, with or without anthracyline, associated with rituximab.[42]

Conclusion

Although the WHO lymphoma classification has provided significant advances in defining MZL, several issues regarding the clinical course of these lymphomas remain to be defined. Collaboration of clinicians and pathologists in defining stringent diagnostic criteria, will help in designing prospective clinical trials to define the optimal therapeutic approach to these diseases.

References

1. Maes B, De Wolf-Peeters C. Marginal zone cell lymphoma—an update on recent advances. Histopathology. 2002;40:117-126.
2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American Classification of lymphoid neoplasms. A proposal from the International Lymphoma Study Group. Blood. 1994;84:1361-1392.
3. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours: Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2001.
4. Mulligan SP, Matutes E, Dearden C, Catovsky D. Splenic lymphoma with villous lymphocytes. Natural history and response to therapy in 50 cases. British Journal of Haematology. 1991;78:206-209.
5. Troussard X, Valensi F, Duchayne E, et al. Splenic lymphoma with villous lymphocytes: clinical presentation, biology and prognostic factors in a series of 100 patients. Groupe Francais d'Hematologie Cellulaire (GFHC). Br J Haematol. 1996;93:731-736.
6. Thieblemont C, Felman P, Callet-Bauchu E, et al. Splenic marginal-zone lymphoma: a distinct clinical and pathological entity. Lancet Oncol. 2003;4:95-103.
7. Nathwani B, Anderson J, Armitage J, et al. Marginal zone B-cell lymphoma: A clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1999;17:2486-2492.
8. Berger F, Felman P, Thieblemont C, et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood. 2000;95:1950-1956.
9. Farinha P, Gascoyne R. Helicobacter pylori and MALT Lymphoma. Gastroenterology. 2005;128:1579-1605.
10. Cerroni L, Zochling N, Putz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. J Cutan Pathol. 1997;24:457-461.
11. Lecuit M, Abachin E, Martin A, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. N Engl J Med. 2004;350:239-248.
12. Ferreri A, Guidoboni M, Ponzoni M, et al. Evidence for an association between *Chlamydia psittaci* and ocular adnexal lymphomas. J Natl Cancer Inst. 2004;96:586-594.
13. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood. 2003;101:2489-2495.
14. Arcaini L, Paulli M, Boveri E, et al. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Cancer. 2004;100:107-115.
15. Pinotti G, Zucca E, Roggero E, et al. Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. Leuk Lymphoma. 1997;26:527-537.
16. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analsyis of 108 patients. J Clin Oncol. 1997;15:1624-1630.
17. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood. 2000;95:802-806d.
18. Copie-Bergman C, Gaulard P, Lavergne-Slove A, et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. Gut. 2003;52:1656.
19. Conconi A, Martinelli G, Thieblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003;15:2741-2745.
20. Wotherspoon A, Doglioni C, Diss T, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet. 1993;342:575-577.
21. Roggero E, Zucca E, Mainetti C, et al. Eradication of *Borrelia burgdorferi* infection in primary marginal zone B-cell lymphoma of the skin. Hum Pathol. 2000;31:263-268.
22. Bertoni F, Conconi A, Capella C, et al. Molecular follow-up in gastric mucosa-associated lymphoid tissue lymphomas: early analysis of the LY03 cooperative trial. Blood. 2002;99:2541-2544.
23. Tsang R, Gospodarowicz M, Pintilie M, et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys. 2001;50:1258-1264.
24. Schechter N, Portlock C, Yahalom J. Treatment of mucosa-asociated lymphoid tissue lymphoma of the stomach with radiation alone. J Clin Oncol. 1998;16:1916/1921.
25. Hammel P, Haioun C, Chaumette M, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. J Clin Oncol. 1995;13:2524-2529.
26. Martinelli G, Laszlo D, Ferreri A, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-*Helicobacter pylori* therapy. J Clin Oncol. 2005;23:1979-1983.
27. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology. 1992;102:1628-1638.
28. Montalban C, Castrillo J, Abraira V, et al. Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma. Clinicopathological study and evaluation of the prognostic factors in 143 patients. Ann Oncol. 1995;6:355-362.
29. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to *Helicobacter pylori* eradication therapy. Lancet. 2001;357:39-40.
30. Levy M, Copie-Bergman C, Gameiro C, et al. Prognostic value of translocation t(11;18) in tumoral response of low-grade gastric lymphoma of mucosa-associated lymphoid tissue type to oral chemotherapy. J Clin Oncol. 2005;23:5061-5066.
31. Thieblemont C, Felman P, Berger F, et al. Treatment of splenic marginal zone B-cell lymphoma: an analysis of 81 patients. Clin Lymphoma. 2002;3:41-47.
32. Talamini R, Montella M, Crovatto M, et al. Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy. Int J Cancer. 2004;110:380-385.
33. Hermine O, Lefrere F, Bronowicki J, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med. 2002;11:89-94.
34. Chacon J, Mollejo M, Munoz E, et al. Splenic marginal zone lymphoma: clinical characteristics and prognostic factors in a series of 60 patients. Blood. 2002;100:1648-1654.
35. Catovsky D, Matutes E. Splenic lymphoma with circulating villous lymphocytes/splenic marginal-zone lymphoma. Semin Hematol. 1999;36:148-154.
36. Franco V, Florena A, Stella M, et al. Splenectomy influences bone marrow infiltration in patients with splenic marginal zone cell lymphoma with or without villous lymphocytes. Cancer. 2001;91:294-301.
37. Lefrere F, Hermine O, Belanger C, et al. Fludarabine: an effective treatment in patients with splenic lymphoma with villous lymphocytes. Leukemia. 2000;14:573-575.
38. Lefrere F, Hermine O, Francois S, et al. Lack of efficacy of 2-chlorodeoxyadenoside in the treatment of splenic lymphoma with villous lymphocytes. Leuk Lymph. 2000;40:113-117.

39. Camacho FI, Mollejo M, Mateo MS, et al. Progression to large B-cell lymphoma in splenic marginal zone lymphoma—a description of a series of 12 cases. Am J Surg Pathol. 2001;25:1268-1276.
40. Neubauer A, Thiede C, Morgner A, et al. Cure of Helicobacter pylori infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. J Natl Cancer Inst. 1997;89:1350-1355.
41. Berger F. The different entities and diagnostic problems. Educational Program of the European Hematology Association meeting. Birmingham. 2000;5.
42. Koh L, Lim L, Thng C. Retreatment with chimeric CD 20 monoclonal antibody in a patient with nodal marginal zone B-cell lymphoma. Med Oncol. 2000;17:225-228.
43. Hyjek E, Isaacson P. Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. Hum Pathol. 1988;19:1315-1326.
44. Hyjek E, Smith W, Isaacson P. Primary B cell lymphoma of salivary glands and its relationship to myoepithial sialadenitis. Hum Pathol. 1988;19:766-776.
45. Zucca E, Bertoni F, Roggero E, Cavalli F. The gastric marginal zone B-cell lymphoma of MALT type. Blood. 2000;96:410-419.