Original Article

Marginal Zone Lymphoma

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Key Words

Marginal zone lymphoma, MALT lymphoma, splenic marginal zone lymphoma, nodal marginal zone lymphoma

Abstract

Marginal zone lymphomas (MZLs) comprise 3 distinct entities: extranodal MZL of mucosa-associated lymphoid tissue (MALT), splenic MZL, and nodal MZL. Gastric MALT lymphoma is the most common extranodal MZL and often develops as a result of chronic *Helicobacter pylori* gastritis. Such cases frequently respond to antibiotics directed against *H. pylori*. Antigen-driven lymphomatous disease can also be seen in the association of *Borrelia burgdorferi* with MALT lymphoma of the skin, *Chlamydia psittaci* with MALT lymphoma of the ocular adnexa, *Campylobacter jejuni* with immunoproliferative disease of the small intestine, and hepatitis C with splenic MZL. This article discusses the pathogenesis and clinical features of MZL and the treatment options available to patients. (*JNCCN* 2006;4:311–318)

In 1994, the Revised European-American Lymphoma classification (REAL)[1] first recognized marginal zone lymphoma (MZL) as consisting of 3 similar types of lymphoma: low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), nodal MZL (NMZL), and primary splenic MZL (SMZL) with or without villous lymphocytes. Several cytogenetic and molecular genetic observations have since confirmed the 3 distinct subtypes according to the World Health Organization (WHO) classification of 2001.[2]

Recently, this group of lymphomas has attracted increasing attention particularly because of an apparent etiologic relationship among some of these tumors and inflammatory conditions or infectious organisms. The most common of the 3 subtypes is extranodal MZL of MALT type, which represents 8% of non-Hodgkin lymphomas.[3] Gastric MALT lymphoma (GML) is the prototype of this entity, with considerable data describing its association with chronic gastritis secondary to *Helicobacter pylori*. The other MZL subtypes are less common, with SMZL and NMZL each composing less than 1% of all lymphomas.

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Extranodal MZL of MALT Type

Isaacson and Wright[4] first described MALT lymphoma in 1983. Since then, the unique pathogenesis of disease, which is related to antigen-induced proliferation of lymphoid tissue, has received increasing attention. MALT can be found in 2 situations. The usual and normal form consists of lymphoid tissue present in specific areas in the gut, such as Peyer patches. The second situation, in which lymphoid tissue proliferates outside the peripheral lymphoid system, is an acquired abnormality that results from chronic inflammation in response to either an infectious agent such as *H. pylori* or an autoimmune process such as myoepithilial sialadenitis associated with Sjögren syndrome.[5]

GML: General Concepts of Pathogenesis

Although MALT lymphoma can involve various tissues, including ocular adenexa, lung, breast, and skin, the most common and well-characterized type is GML, which is associated with *H. pylori* chronic gastritis. The infection is found in the gastric mucosa of most patients with GML.[6–8] Considerable evidence suggests that antigenic stimulation of B cells by *H. pylori* is essential to the development and persistence of GMLs. Before the development of lymphoma, *H. pylori* induces a proliferation of lymphoid tissue that is not native to gastric mucosa, resulting in chronic gastritis.[9] This chronic antigenic stimulation may lead to the selective expansion of a monoclonal B-cell population as a precursor to MALT lymphoma. In fact, a dominant B-cell clone has been found in biopsies

performed on patients with *H. pylori*–positive chronic gastritis who later developed GML.[6]

Genetic analysis of immunoglobulin genes provides further evidence for the antigenic stimulation of MALT lymphoma clones. When naïve B cells are activated by antigen, they undergo a process termed *somatic hypermutation* in which the immunoglobulin variable region—specifically the complementarity-determining regions of the DNA that code for the antibody-binding site—is rearranged in an attempt to select a B-cell clone, making antibody with the highest affinity for the antigen in question. Nucleotide sequence analysis of the immunoglobulin heavy-chain variable (IgV_H) regions of MALT lymphoma cells confirms the presence of somatic hypermutation, suggesting that the tumor cells have been selected through their exposure to antigen.[10] Some experts suggest GML clones are dependent on persistent antigenic stimulation by *H. pylori*, and therefore the tumor frequently remains localized to the gastric mucosa where *H. pylori* is harbored. In contrast, in the disseminated state, the tumor has usually transformed or changed to a more aggressive form that is antigen-independent and less likely to respond to eradication of *H. pylori* infection.

GML: Pathologic Characteristics

A spectrum of pathologic change occurs during the transition from *H. pylori* gastritis to MALT lymphoma, making the diagnosis of early lymphoma difficult.[11] Histologic characteristics that are useful in diagnosing low-grade GML include prominent lymphoepithelial lesions, moderate cytologic atypia of neoplastic lymphocytes, and plasma cells with Dutcher bodies, although the absence of these criteria does not exclude lymphoma.[12] The presence of monoclonal B cells, although consistent, is not in itself proof of MALT lymphoma, because premalignant *H. pylori* chronic gastritis may also demonstrate monoclonal B cells,[10] as do 50% of histologically normal gastric mucosa biopsies after complete regression of GML treated successfully with an anti–*H. pylori* regimen.[13]

GML: Molecular Abnormalities

The pathogenesis of MALT lymphomas has been further elucidated by the understanding of molecular and genetic abnormalities, which may also aid in the diagnosis and prediction of response to treatment. The most common chromosomal abnormality described is the t(11;18)(q21;q21) translocation, occurring in 18% to 32% of patients with GML.[14–17] This translocation is specific to MALT lymphomas and is not found in NMZLs or SMZLs. When the t(11;18) translocation is found, it is usually the only chromosomal abnormality and is more frequently associated with locally advanced lymphomas. In the stomach, t(11;18) translocation identified 63% of *H. pylori*–negative MALT lymphomas and 70% to 100% of MALT lymphomas unresponsive to *H. pylori* treatment.[14,17] Thus, this translocation is clearly associated with *H. pylori* antigenic independence in GMLs. Two genes are involved in the t(11;18) translocation: the *API2* gene, localized to the breakpoint on chromosome 11; and the *MALT1* gene, localized to the breakpoint on chromosome 18. The translocation produces API2-MALT1, a fusion protein that enhances nuclear factor-κB (NF-κB) activity, leading to failure of apoptosis and other consequences.

Less common genetic aberrations include the t(14;18)(q32;q21) translocation, which occurs in 15% to 20% of MALT lymphomas and brings the *MALT1* gene downstream of the IgH enhancer. This translocation is more common in nongastrointestinal MALT lymphomas, primarily involving lung, liver, and ocular adenxa, and is often associated with other genetic aberrations.

An additional chromosomal translocation, t(1;14)(p22;q32), occurs in 1% to 2% of MALT lymphomas and is also associated with nongastrointestinal types. This translocation brings the *bcl10* gene under the control of the IgH enhancer of chromosome 14, resulting in an overexpression of *bcl10*, leading to activation of NF-κB. The t(1;14) translocation is specific to MALT lymphomas, and, like the t(11;18) translocation, identifies tumors unlikely to respond to antibiotic treatment for *H. pylori*.[18]

These data indicate that GMLs develop along 2 distinct major molecular pathways, both arising from chronic gastritis.[19] The first group of tumors involves t(11;18), which is relatively *H. pylori*–independent, rarely accumulates additional genetic aberrations, and generally does not transform into diffuse large B-cell lymphoma. The second group lacks t(11;18) and tends to be *H. pylori*–dependent. This group may accumulate genetic aberrations in time, such as trisomy 3 and 18, translocations involving *bcl10* and *MALT1*, and other molecular alterations, and can eventually lead to transformation into diffuse large B-cell lymphoma.[20]

GML: Presenting Symptoms and Staging Evaluation

The presenting symptoms of patients with MALT lymphoma depend on the sites where lymphomatous disease occurs, such as the lung, breast, orbital adenexa, skin, or gastrointestinal tract. Systemic B-stage symptoms such as fever, night sweats, or weight loss are unusual. Patients with GML often present with nonspecific symptoms, most commonly dyspepsia or epigastric pain. A definitive mass may be absent on endoscopy, whereas gastritis or ulceration is more commonly seen, often with raised ulcer borders. The lactate dehydrogenase and β_2-microglobulin levels are usually within the normal range. The revised Blackledge staging system is often employed, which takes into account the depth of tumor involvement and extent of local lymph node involvement.[21] Active *H. pylori* infection should always be confirmed by histology or other objective studies because its presence is important in treatment and prognosis.

GML: Treatment

Most experts agree that the first-line treatment of patients with *H. pylori*–positive GML confined to the stomach should be antibiotic therapy to eradicate *H. pylori*. Considerable evidence indicates a durable remission of the lymphoma in 60% to 80% of these patients.[11,22–24] Time to remission is generally longer than with other low-grade lymphomas treated with chemotherapy. It can usually be documented 6 months after *H. pylori* eradication, although remissions occurring after more than 1 year from antibiotic therapy have been reported. Response to *H. pylori* eradication may be predicted by the extent of disease, with earlier lesions having the best response rates. In one series, cases confined to the mucosa and submucosa showed a histologic complete remission (CR) rate of 70%, whereas cases that were locally advanced to the muscularis mucosae, the serosa, or the perigastric lymph nodes showed a significantly lower CR rate of 38%.[22]

Although successful use of antibiotic therapy directed against *H. pylori* has occurred primarily in low-grade GMLs, one series of patients with *H. pylori*–positive diffuse large B-cell lymphoma shows that antibiotic therapy was successful in inducing CRs of the gastric lymphoma in 7 of 8 cases.[25]

Various *H. pylori* eradication regimens have been used successfully. Common regimens include a twice-daily proton pump inhibitor, bismuth subsalicylate, and a combination of the following options: 1) amoxicillin plus clarithromycin; 2) tetracycline plus clarithromycin; and 3) tetracycline plus metronidazole. One study used 2 courses of antibiotics: an initial 21-day course that was repeated 8 weeks later.[26] In this group, only 1 of 28 *H. pylori*–positive patients remained positive by histology after the initial course, thus benefiting from the second course, which eradicated the organism. Nonetheless, the response rates in this group were similar to those in other reports that employed only a single course of antibiotic treatment. Most experts agree that a single course of anti–*H. pylori* therapy, followed up closely, is sufficient to document eradication of the organism.

In early-stage disease, resistance of GMLs to *H. pylori* eradication can be predicted by the t(11;18)(q21;q21) translocation. In a series of GML patients with successful *H. pylori* eradication, 47 of 48 patients experienced a CR and 43 of 63 patients with no response had stage IE disease. The translocation t(11;18) was detected in 2 of 48 (4%) patients who experienced CR and in 42 of 63 (67%) patients who did not show response, including 60% with stage IE.[27] Despite the efficacy of *H. pylori* eradication in the treatment of antigen-dependent MALT lymphoma, a significant group of patients do not show response to treatment. Further genetic aberrations have led to antigen independence in these patients. Therefore, strict endoscopic monitoring is recommended after *H. pylori* treatment to document eradication of *H. pylori*. Re-treatment is indicated if eradication is not experienced. Endoscopic monitoring should also be performed to determine response to therapy and to identify patients without response who will require alternative therapies. However, response to antibiotic therapy can occur very slowly.

H. pylori–negative lymphomas generally do not respond to *H. pylori* eradication therapy and are considered *H. pylori*–independent.[22] No consensus exists concerning the optimal treatment for patients whose disease does not respond to *H. pylori* eradication or for the subset of *H. pylori*–negative cases. No randomized trials have been completed for this group. Nonetheless, successful therapy has been described in patients treated with chemotherapy, radiotherapy, or surgery (Table 1). Involved-field radiation therapy has been associated with 100% histologic CR and 100% event-free survival after a median follow-up of 27 months in one report and 5 years in another.[28,29] Although surgery has been successful in the past,[30] it

Table 1 Gastric Mucosa-Associated Lymphoid Tissue Lymphoma: Treatment of anti-*Helicobacter pylori* Therapy-Refractory, Relapsed, and *H. pylori*–Negative Patients

Study	Patient Types	Treatment Type	Patients, *n*	Overall Response	Complete Remission	Response Duration
Levy et al.[17]	t(11;18)-positive	Oral alkylators*	12	5 (42%)	0	1/8 in remission at 7 years
	t(11;18)-negative	Oral alkylators*	9	8 (89%)	2	8/9 in remission at 7 years
Jager et al.[31]	Stage IE, anti-*H. pylori* therapy refractory or higher stage	Cladribine†	18	18 (100%)	100%	3/18 relapses with 32 months median follow-up
Martinelli et al.[32]	*H. pylori* (+) or (–) relapsed/ refractory to prior treatment‡	Rituximab 375 mg/m^2 weekly × 4	27	20/26 (77%)	12/26 (46%)	2/26 relapsed with 33 months median follow-up
de Mascarel et al.[30]	Anti-*H. pylori* therapy refractory	Surgery	28	28 (100%)	100%	21 patients followed—all in complete remission at median 25.9 months follow-up
Tsang et al. [29]	*H. pylori* (–) or anti-*H. pylori* therapy refractory	Radiation§	13	13 (100%)	100%	Failure-free remission 100% at 5 years

*Cyclophosphamide 100 mg/d (3 patients) or chlorambucil 6 mg/m^2/d, 14 d/mo.
†Cladribine 0.12 mg/kg days 1–5, given every 4 weeks for 6 cycles.
‡11 *H pylori*–positive, relapsed/refractory to anti-*H. pylori* therapy ± chemotherapy; 16 *H. pylori*–negative: 2 first-line rituximab, 14 relapsed/refractory to anti-*H. pylori* therapy, chemotherapy, or surgery.
§Median of 25 Gy (range 20 to 35 Gy), 3 patients also treated with chemotherapy.

currently has a limited role in GML because of the success of more conservative treatments.

The use of chemotherapy for GML is expanding steadily. The oral alkylators cyclophosphamide and chlorambucil, taken for 12 to 18 months, were shown to induce a durable remission confirmed at 7 years' follow-up in 8 of 9 cases that were t(11;18) translocation–negative.[17] The same series reported partial remissions in 5 of 11 t(11;18) translocation–positive cases, only one of which persisted for the 7 years of follow-up. Other studies have confirmed the activity of purine analogues, including a 100% histologic CR in 19 GML cases treated with cladribine.[31] Rituximab, the anti-CD20 monoclonal antibody, has shown efficacy in refractory or relapsed GML, with an overall response rate of 77% and pathologic CR rate of 46%.[32] Because of this high degree of efficacy and its minor toxicity, rituximab should be studied further. The proteasome inhibitor bortezomib inhibits NF-κB, which is the downstream effector of the several chromosomal translocations discussed earlier. Several cases of MZL have responded to bortezomib in phase II studies of indolent lymphomas, but further studies are needed to define efficacy.[33]

Other MALT Lymphomas

Although GML is the best described site of disease in MALT lymphoma, the tumor may also occur in other extranodal sites that are often associated with specific infectious organisms. Extranodal MALT lymphomas have occurred in the skin, small intestine, thyroid, ocular adnexal structures, breast, and lung.

Immunoproliferative disease of the small intestine (IPSID) was not originally considered a true malignant lymphoma by the 1978 World Health Organization (WHO).[34] More recently, however, IPSID has been considered a variant of MALT lymphoma,[35] with predominant involvement of the proximal small intestine and symptoms of chronic diarrhea and abdominal pain.[36] It mainly affects young adults, and most cases are reported in the Middle East, North and South Africa, and the Far East.[37,38] Recently, *Campylobacter jejuni* was identified in the intestinal

tissue of a patient with IPSID, who responded well to antibiotic treatment.[39] *C. jejuni* was confirmed in archival intestinal biopsy specimens of 4 of 6 additional patients, suggesting that the organism may be the antigenic stimulus that induces IPSID. Even before the characterization of this organism, the response of IPSID to antibiotic treatment, such as tetracycline or metronidazole taken for 6 months, was well documented, with CR in 30% to 70% of reported cases.[40,41]

In cutaneous MALT lymphoma, *Borrelia burgdorferi* may be the inciting antigen in at least a subset of cases.[42,43] Tissue biopsies in patients with cutaneous MZL have shown the spirochete, and antibiotic therapy to eradicate the microorganism can induce CR.[44] The *Chlamydia psittaci* organism has been detected in 80% of cases of ocular adnexal MZL.[45] In a recent series, 7 of 9 patients with ocular adnexal MZL who were treated with doxycycline for 3 weeks experienced objective lymphoma response.[46]

These cases show that MALT lymphoma may arise as a consequence of antigenic stimulation and may be successfully eradicated through treatment directed against the offending antigen. Nonetheless, further prospective clinical trials are needed to confirm the reported therapeutic responses.

SMZL

SMZL, first recognized as a specific entity in the 2001 WHO classification,[2] is recognized as the same entity as splenic lymphoma with villous lymphocytes (SLVL) with varying levels of circulating cells.[47] SMZL occurs in older adults at a median age of 65 years. Most patients present with symptoms of abdominal discomfort from massive splenomegaly, but B-stage symptoms and symptomatic anemia are also common. Autoimmune processes are found in 10% to 15% of cases, including autoimmune hemolysis and immune thrombocytopenia.[48] A serum monoclonal paraprotein, commonly of immunoglobulin M type, is seen in 10% to 25%. Between 50% and 70% of cases will have peripheral blood involvement with lymphocytosis, although a higher rate of involvement may be confirmed by flow cytometry.[48–50] Bone marrow involvement with characteristic pathologic findings is reported in 83% to 100%, which allows SMZL to be diagnosed through biopsy of bone marrow rather than requiring splenectomy for diagnosis.[51] Several studies have reported liver involvement in 20% to 30% of patients, described as nodular infiltration of portal tracts or lobular invasion.[48,50]

In contrast to the well-characterized chromosomal aberrations of MALT lymphomas, SMZLs do not have unique cytogenetic or molecular identifiers. Instead, SMZLs are more heterogeneous, with chromosomal gains or losses in 83% of patients and a median of 4 chromosomal aberrations per case.[52,53] The t(11;18)(q21;q21) and t(14;18)(q32;q21) translocations, which are the most common genetic aberrations in GMLs, have not yet been reported in SMZL.[53,54] Recurring clonal abnormalities in SMZLs include trisomy 3, found in 15% to 36% of cases using interphase fluorescence in situ hybridization,[55,56] and 7q deletion, reported in 26% to 40% of cases using cytogenetic analysis and in even higher rates using microsatellite markers.[57] Molecular heterogeneity has also been noted, with the absence of somatic hypermutation of the IgV_H in 49% of SMZLs, indicating the involvement of an antigen-naïve B-cell clone in half the cases. Interestingly, the group with unmutated IgV_H had a more aggressive clinical course and significantly shorter overall survival.[58]

The association of hepatitis C virus (HCV) infection with non-Hodgkin lymphoma is well established, with one study documenting 26% of patients with non-MALT MZL testing positive for the virus.[59] Mixed cryoglobulinemia, an extrahepatic manifestation of HCV infection, is associated with monoclonal populations of B cells, and is often associated with HCV-related SMZL. A study of 18 cases of SMZL with concomitant HCV infection reported the presence of type II mixed cryoglobulinemia (MC) in all 18 cases, which suggests the monoclonal B-cell clones in MC may be a premalignant lesion.[60] In one series of SMZL, patients with HCV infection were treated with interferon (IFN)-α2b alone or in combination with ribavirin, resulting in a CR in 7 of 9 cases. All 7 also had a sustained virologic response with an undetectable HCV viral load. The role of anti-HCV treatment in HCV-related low-grade lymphomas was confirmed in 13 patients in whom hematologic response was correlated with virologic response.[61]

Patients with SMZL who are HCV-negative do not require immediate treatment if they are asymptomatic and do not experience significant cytopenias.[50,62] The clinical course of SMZL is indolent, with 88% of untreated patients experiencing a 5-year overall survival rate.[49] When treatment is needed, it is usually

because of symptomatic splenomegaly or cytopenias. Experts generally agree that splenectomy is the best initial therapy in this circumstance. Splenectomy alone produces long-term improvements in cytopenias and relief of abdominal discomfort.[49] In one series, all 16 patients who underwent splenectomy experienced improvement in cytopenias and did not require further treatment until after more than 5 years.[63]

Splenic radiation may be a viable option for symptomatic patients who cannot undergo splenectomy or who have contraindications to chemotherapy. Experience with splenic radiation is limited, but reports have shown improved local and systemic symptoms using this approach.[49,64]

Chemotherapy can be used in patients who have contraindications to splenectomy or have experienced relapse after splenectomy. However, when used as first-line therapy, alkylating agents such as chlorambucil or cyclophosphamide have been associated with only minor efficacy. Patients treated for progression after splenectomy may experience better response to alkylating agents alone or in combination with other drugs, with a 64% 5-year overall survival.[49] Purine analogues are promising, with various series showing that fludarabine results in clearance of peripheral villous lymphocytes and normalization of cytopenias.[65,66] Cladribine has also been associated with efficacy in alkylator-refractory cases, although one series reported a high rate of treatment-related toxicity.[67,68]

In patients with SMZL, preliminary reports using rituximab, the monoclonal antibody against CD-20, indicate excellent responses, both when used alone and in combination with chemotherapy.[69,70]

NMZL

NMZL classically involves primarily the peripheral lymph nodes in the neck, axilla, or inguinal regions, usually with no involvement of extranodal sites.[71] Clinical information on NMZL is sparse, and most knowledge of this MZL type is derived from pathologic series rather than clinical reports.[72,73] Compared with extranodal MZL of MALT type, NMZL presents at a later stage, with 71% of patients stage III and IV at diagnosis, and has a worse prognosis, with a 5-year overall survival rate of 56%. Treatment options include single-agent chlorambucil or fludarabine or combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or similar regimens. CRs in as many as 69% of cases have been reported, although the median time to progression in the same series was only 1.3 years.[50] Reports also show efficacy using rituximab as a single agent.[73] Younger patients with poor prognostic factors may also be treated effectively with high-dose chemotherapy and autologous stem cell transplantation.[50] Prospective studies have not yet been performed on this entity, and treatment decisions should be based on individual patient characteristics.

Summary: MZLs as Examples of Antigen-Driven Processes

The close relationship between infectious organisms and development of MZL is now well appreciated. In GML, the evidence is strong that *H. pylori* is an antigenic stimulus of B cells, leading to the induction of the lymphoma. Nonetheless, the existence of *H. pylori*–negative GML and the unresponsiveness of early-stage t(11;18) translocation–positive GML to antibiotic treatment suggests either an antigen-independent subgroup, or presence of a yet unidentified pathogen. The association of *B. burgdorferi* with MALT lymphoma of the skin, *C. psittaci* with MALT lymphoma of the ocular adenexa, *C. jejuni* with the MALT variant IPSID, and hepatitis C virus with SMZL all confirm the concept of antigen-driven lymphomatous disease. The fact that these malignant lymphomas may respond to antibiotic or antiviral therapy directed specifically against the etiologic organism makes clinical and biological understanding of these disorders even more important.

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