

State-of-the-Art Therapeutics: Marginal-Zone Lymphoma

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A B S T R A C T

Marginal-zone lymphomas comprise the mucosa-associated lymphoid tissue (MALT) type (extranodal marginal-zone lymphoma [EMZL]), the nodal marginal zone B-cell lymphoma (NMZL) and the splenic MZL (SMZL). EMZL is relatively common, whereas the remaining two entities are relatively rare disorders. EMZL, especially in its gastric localization, is the most studied MZL, and there are many data both on the underlying genetic lesions and on the role of infectious agents. These data have determined unique approach among all other lymphoma subtypes: the possibility of treating a subset of patients with antibiotics alone as first line of treatment. Indeed, there is compelling evidence that histologic regressions can be achieved in most gastric MALT lymphomas by eradicating *Helicobacter pylori* infection. However, molecular follow-up studies showed the persistence of the malignant clone in half of the cases in histologic remission after antibiotic treatment and transient, either histologic or molecular, relapses have been reported, too. Hence, a careful long-term follow-up is mandatory after antibiotic treatment. Radiotherapy, chemotherapy, anti-CD20 monoclonal antibodies are effective alternative therapies. The precise role of surgical resection should be redefined in view of the encouraging results of conservative approaches. Differently from EMZL, both SMLZ and NMZL often present with disseminated disease at diagnosis. The therapeutic approach comprises splenectomy, for SMZL, and chemotherapy, but with no consensus about the best treatment. This review addresses the current knowledge on the clinical features and therapeutic approaches for the individual MZLs.

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INTRODUCTION

The term marginal-zone lymphoma (MZL) was proposed in the Revised European American Lymphoma classification (REAL)¹ to comprise two apparently closely related lymphoma subtypes: the low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, currently named MALT lymphoma, and the nodal marginal zone B-cell lymphoma, also known as monocytoid lymphoma. A third MZL subtype, immunophenotypically similar but with distinct clinical and morphologic features, was also provisionally included in the REAL classification (ie, the primary splenic MZL with or without villous lymphocytes.) At that time the available cytogenetic data

suggested that these three lymphomas shared similar cytogenetic alterations. Several important cytogenetic and molecular genetic observations have subsequently revealed that each is a distinct disorder and now each is considered a separate subtype in the WHO classification.²

Although splenic and nodal MZL are uncommon disorders, each comprising less than 1% of lymphomas, the extranodal MZL of MALT type is not rare.³ In a survey of more than 1,400 non-Hodgkin's lymphomas from nine institutions in the United States, Canada, the United Kingdom, Switzerland, France, Germany, South Africa, and Hong Kong, this entity represented approximately 8% of the total

number of cases, including both the common gastrointestinal and the less usual nongastrointestinal localizations.³

MALT LYMPHOMA

Clinical Features and Diagnostic Evaluation

The presenting symptoms of MALT lymphomas are nonspecific and mainly related to the primary location.^{4,5} Few patients present with elevated lactate dehydrogenase (LDH) or beta-2-microglobulin levels. Constitutional “B” symptoms are exceedingly uncommon. MALT lymphoma usually remains localized for a prolonged period within the tissue of origin, but dissemination to multiple mucosal sites is not uncommon, especially in nongastrointestinal MALT lymphomas, in which about one fourth of cases have been reported to present with involvement of multiple mucosal sites or nonmucosal sites such as bone marrow.⁵⁻⁷ Within the stomach, low-grade MALT lymphoma is often multifocal and this may explain the report of relapses in the gastric stump after surgical excision.

The staging system for extranodal MZL is controversial.^{5,8} A modified Blackledge staging system is recommended for the cases presenting in the stomach.⁹ Regardless of the presentation site, diagnostic studies should include the standard lymphoma staging procedures with CBCs; basic biochemical studies (including LDH and beta 2-microglobulin); computed tomography of the chest, abdomen, and pelvis; and a bone marrow biopsy. The initial staging should include a gastroduodenal endoscopy with multiple biopsies from each region of the stomach, duodenum, gastroesophageal junction, and from any site that seems abnormal. Fresh biopsy and washings material should be available for cytogenetic studies in addition to routine histology and immunohistochemistry.

A molecular genetic or a fluorescinated in situ hybridization (FISH) analysis for detection of the t(11;18) (q21;q21) API2/MALT1¹⁰⁻¹³ is recommended, and, whenever possible also of the t(14;18)(q32;q21) MALT1/IgH¹³⁻¹⁵ and the t(3;14)(p14.1;q32) FOXP1/IgH.¹⁶ The presence of the t(11;18) correlates with disseminated disease and a lower response to antibiotic therapy.¹⁷⁻¹⁹ While definitive data are lacking for the other translocations, they may become available in the near future.

Histologic features, such as scattered transformed blasts, plasma cell differentiation, presence of reactive T cells, and follicular colonization, suggest that MALT lymphoma cells may be participating in an immunologic process.²⁰ A body of evidence supports the hypothesis that the bacterium *Helicobacter pylori* may provide the antigenic stimulus for promoting and sustaining the growth of gastric lymphoma.^{4,21-25} Other infectious agents have also been implicated in specific extranodal MZL sites. *Borrelia burgdorferi*, the spirochete responsible for Lyme disease, may be implicated in the pathogenesis of at least a subset

of cutaneous marginal zone B-cell lymphomas.^{26,27} The micro-organism has been cultured or its DNA amplified from skin extranodal MZL, and complete remission of lymphoma has been achieved with antibiotics therapy aimed to the spirochete. The presence of *Chlamydia psittaci* has been shown in up to 80% of ocular adnexa lymphomas, and clinical responses have been observed after appropriate antibiotic therapy.^{28,29} The entity known as immunoproliferative small intestine disease (IPSID; also known as α chain disease)^{30,31} is now considered an extranodal MZL associated with *Campylobacter jejuni* infection. This disorder is more frequent in the Middle East, especially the Mediterranean area, where it was established in the 1970s that cases of early IPSID respond to antibiotic treatment. More recently, Lecuit et al³⁰ demonstrated the presence of a specific pathogen in five of seven patients, linking this extranodal MZL to *C jejuni*.

On the basis of these data, appropriate investigations must be performed to show the presence of infectious agents. In particular for gastric MALT lymphomas, the presence of active *H pylori* infection must be determined by histochemistry (Genta stain or Warthin-Starry stain) and breath test; serology is recommended when the results of histology are negative. For other locations of extranodal MZL, an evaluation for infectious agents may be undertaken as noted in the preceding paragraphs but the clinical consequences of the identification of and treatment for *C psittaci* or *B burgdorferi* have not been validated.

In the stomach, an endoscopic ultrasound is recommended in the initial staging for evaluation of depth of infiltration and presence of perigastric lymph nodes. A deep infiltration of the gastric wall is associated with a higher risk of lymph node involvement, and a lower response rate with antibiotic therapy alone.³²⁻³⁵

Treatment

It is generally accepted that eradication of *H pylori* with antibiotics should be employed as the sole initial treatment of gastric MALT lymphoma confined to the gastric wall. This approach has been validated extensively, with more than 20 reported studies.³⁶⁻³⁸ The data are not conclusive regarding the role of adjuvant therapy after antibiotics.³⁹

Regular follow-up after antibiotics is highly advisable because diagnostic gastric biopsies do not completely exclude the presence of a concomitant aggressive diffuse large B-cell lymphoma, which requires cytotoxic therapy with curative intent. We recommend performing a breath test 2 months after treatment to document *H pylori* eradication and repeat post-treatment endoscopies with multiple biopsies every 6 months for 2 years, then yearly to monitor the histologic regression of the lymphoma.

Several groups have confirmed the efficacy of antibiotics in inducing apparently durable lymphoma

remissions: in 60% to 100% of patients with localized *H pylori*-positive gastric MALT lymphoma.^{32,33,35,40-43} The histologic remission can usually be documented within 6 months from the *H pylori* eradication, but the therapeutic response may be delayed up to more than 1 year.⁴ The data regarding *C psittaci* and MALT lymphoma of the ocular adnexa^{28,29} may provide the rationale for the antibiotic treatment of these localized lesions, but this approach remains investigational until confirmed by larger clinical studies.

The interpretation of residual lymphoid infiltration in post-treatment gastric biopsies can be difficult and there are no uniform criteria in the literature for the definition of histologic remission. The Wotherspoon score reported in Table 1 was initially proposed to express the degree of confidence in the diagnosis of MALT lymphoma on small gastric biopsies.²⁵ It has been used to evaluate the response to therapy in some trials but many investigators found it difficult to apply in this setting and other criteria have been proposed.⁴⁰ The lack of standardized and easily reproducible criteria can affect the comparison of the results of the different clinical trials. A novel histologic grading system has been proposed by Copie-Bergman et al⁴⁴ with the aim of providing clinically relevant information to the clinician. This system, which is summarized in Table 2, seems highly reproducible and classifies the histologic features in post-treatment gastric biopsies as “complete histological remission,” “probable minimal residual disease,” “responding residual disease,” and “no change.” Assessing treatment response is of great clinical relevance and this scheme may become a useful tool if its reproducibility is confirmed by further testing on independent series.⁴⁵

After antibiotic treatment for gastric MZL, studies incorporating molecular techniques have shown that histologic and endoscopic remission does not necessarily mean “cure.” The long-term persistence of monoclonal B cells after histologic regression of the lymphoma has been reported in about half of the cases, suggesting that *H pylori*

eradication suppresses but does not eradicate the lymphoma clones.^{43,46,47} The clinical significance of the detection of B-cell monoclonality by molecular methods remains unclear. Histologic evaluation of repeated biopsies remains the fundamental follow-up procedure, despite the reproducibility problems discussed in the preceding paragraphs.

No definite guidelines exist for the management of the subset of *H pylori*-negative cases, for patients who fail antibiotic therapy, and for nongastric locations. A choice can be made between conventional therapeutic modalities but there are no published randomized studies for evidence-based decision making. In two retrospective series of patients with gastric low-grade MALT lymphoma, no statistically significant difference was apparent in survival between patients who received different initial treatments.^{42,48}

Excellent disease control using radiation therapy has been reported by several institutions, supporting the approach that modest dose involved-field radiotherapy (30 Gy administered in 4 weeks of radiation to the stomach and peri-gastric nodes) is the treatment of choice for patients with stage I to II MALT lymphoma of the stomach without evidence of *H pylori* infection or with persistent lymphoma after antibiotics.⁴⁹⁻⁵² Surgery has been used widely and successfully in the past, but the precise role for surgical resection should be redefined currently in view of the promising results of the conservative approach.⁴

Patients with systemic disease should be considered for systemic treatment.⁵³ Few single agents or combination chemotherapy regimens have been tested specifically in MALT lymphomas. Oral alkylating agents (either cyclophosphamide or chlorambucil, with median treatment duration of 1 year) can result in a high rate of disease control.^{54,55} Other phase II studies demonstrated the antitumor activity of the purine analogs fludarabine⁵⁶ and cladribine,⁵⁷ which may be associated with an increased risk of secondary myelodysplastic syndrome,⁵⁸ and of a combination regimen of chlorambucil, mitoxantrone and prednisone.⁵⁹ The anti-CD20 monoclonal antibody

Table 1. The Wotherspoon Histologic Score for Diagnosis and Post-Treatment Evaluation of Gastric MALT Lymphoma (modified from Wotherspoon et al²⁵)

Score	Description	Histologic Features
0	Healthy	Scattered plasma cells in lamina propria
1	Chronic active gastritis	Small clusters of lymphocytes in lamina propria; no LELs
2	Chronic active gastritis with lymphoid follicles	Prominent lymphoid follicles with surrounding mantle zone and plasma cells; no LELs
3	Suspicious lymphoid infiltrate, probably reactive	Lymphoid follicles surrounded by small lymphocytes that infiltrate diffusely in lamina propria and occasionally into epithelium
4	Suspicious lymphoid infiltrate, probably lymphoma	Lymphoid follicles surrounded by CCL cells that infiltrate diffusely in lamina propria and into epithelium in small groups
5	Low-grade MALT lymphoma	Dense diffuse infiltrate of CCL cells in lamina propria with prominent LELs

Abbreviations: MALT, mucosa-associated lymphoid tissue; LEL, lymphoepithelial lesion; CCL, centrocyte-like.

Table 2. The GELA Histologic Grading System for Post-Treatment Evaluation of Gastric MALT Lymphoma (modified from Copie-Bergman et al⁴⁴)

Score	Description	Histologic Features
CR	Complete histologic remission	Normal or empty LP and/or fibrosis with absent or scattered plasma cells and lymphoid cells in the LP; no LELs
pMRD	Probable minimal residual disease	Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM; no LELs
rRD	Responding residual disease	Focal empty LP and/or fibrosis; dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP. Focal LELs or absent
NC	No change	Dense, diffuse or nodular lymphoid infiltrate with LELs (LELs "may be absent")

Abbreviations: GELA, Groupe d'Etude des Lymphomes de l'Adulte; MALT, mucosa-associated lymphoid tissue; LP, lamina propria; LEL, lymphoepithelial lesion; MM, muscularis mucosa; SM, submucosal.

rituximab is effective in MZL with a reported response rate of about 70%, representing an additional option for the treatment of systemic disease.^{60,61} Another potentially active class of anti-cancer agents drugs are those targeted to the inhibition the NF κ B (necrosis factor kappa B) pathway, the common target of the recurrent translocations. An example of this class is bortezomib that is currently being tested in clinical trials specifically designed for patients with MALT lymphoma.

SPLenic MZL

Most patients with splenic MZL (SMZL) are more than 50 years old.⁶²⁻⁶⁶ The disease usually presents with massive splenomegaly, abdominal discomfort, and pain. Diagnosis is often made at splenectomy, performed to establish the cause of unexplained spleen enlargement. B symptoms are present in 25% to 60% of cases; anemia, thrombocytopenia, or leukocytosis are reported in approximately 25% of cases. Autoimmune hemolytic anemia is not uncommon, being found in up to 15% of patients. Peripheral lymph node involvement is typically absent, while splenic hilar lymph nodes are involved in about 25% of cases. Approximately 30% of cases have liver involvement. Nearly all patients have infiltrated bone marrow, often accompanied by involvement of peripheral blood. Serum paraproteinemia, most frequently of immunoglobulin M type, is observed in about 10% to 25% of cases, and this can pose a problem in the differential diagnosis with lymphoplasmacytic lymphoma or Waldenström macroglobulinemia.^{2,63-65}

In advanced stages of splenic, nodal, or extranodal MZL, the presence of disseminated disease with concomitant splenic, extranodal, and nodal involvement makes a precise diagnosis of the MZL subtype difficult. The clinical course of SMZL is usually indolent with 5-year overall survival ranging from 65% to 80%. Most cases can be managed safely with an initial watchful-waiting policy.^{63,65,67,68} When treatment is needed, this is usually because of symptomatic splenomegaly or cytopenias. Splenectomy is the treatment of choice. It results in a reduction or disappearance of circulating tumor lymphocytes and recovery of the lymphoma-associated cytopenias. The benefit of splenectomy often persists for several years and time to next treatment

can be more than 5 years in the cases where lymphocytosis persists and or progresses after splenectomy. Adjuvant chemotherapy after splenectomy may result in higher rate of complete responses, but there is no evidence of a survival benefit.⁶⁸

Chemotherapy alone may be considered for patients who require treatment but have contraindication to splenectomy, and also for patients with clinical progression after splenectomy. Alkylating agents and fludarabine have been reported to be active and can be used as single agents or in combination. Rituximab, alone or in combination with chemotherapy, has been reported to induce responses in cases refractory to standard chemotherapy in individual cases.⁶⁸⁻⁷⁰ Treatment of hepatitis C (HCV) infection with interferon alfa alone or in combination with ribavirin may be helpful for the patients with splenic lymphoma with villous lymphocyte and HCV infection.⁷¹⁻⁷⁴

NODAL MZL

The clinical data for management of nodal MZL (monocytoid lymphoma) are sparse and drawn largely from pathologic series rather than clinical centers.^{75,76} The median age at presentation is in the sixth decade. The most common presenting feature is a localized adenopathy, most often in the neck. Currently there is no consensus regarding the best treatment; individual cases are managed differently according to site and stage. Treatment options include single-agent chlorambucil or fludarabine or combination chemotherapy regimens. Rituximab may also have some efficacy⁷⁷ and anti-HCV treatment may induce lymphoma regression in some HCV-infected patients.⁷² Autologous transplantation has been used in younger patients with adverse prognostic factors and high number of large cells.⁶⁴ However, no prospective studies have been conducted so far and treatment decision should be based on the histologic and clinical features of the individual patient.^{78,79}

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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