Purine analogs in marginal-zone lymphomas

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Summary
In an area of lymphoma classification still being defined, marginal-zone lymphomas have distinctive immunohistochemical and cytogenetic features that distinguish them from mantle-cell and follicular lymphomas. There are three subtypes: the extranodal mucosa-associated lymphoid tissue (MALT) lymphomas, the nodal monocytoid B-cell (MBCL) lymphomas, and the splenic marginal-zone lymphomas. The MALT lymphomas represent the neoplastic counterpart of the gut-associated lymphoid tissue, which extends from the jejunum to the rectum. They arise in sites usually containing no lymphoid tissue, such as the stomach, thyroid, and salivary gland. Gastric MALT lymphomas, the most common, are associated with Helicobacter pylori. The MBCL lymphomas closely resemble MALT lymphomas and unlike other non-Hodgkin's lymphomas are commonly composite. Therapy for these lymphomas may include radiation therapy or surgery when disease is of limited extent. However, gastrectomy for gastric MALT lymphomas is not favored because of the efficacy of antibiotic regimens that can eliminate H. pylori infection. Splenectomy may be indicated for splenic lymphomas. Purine analogs are promising therapeutic agents because they are specific for lymphoid cells. Also, they may prove useful in indolent cancers such as these, because of their activity against dividing and resting cells. Purine analogs may be considered as second-line therapy after alkylating agents for these lymphomas.

Key words: MALT lymphomas, marginal-zone lymphomas, monocytoid B-cell lymphomas, purine analogs

Introduction
The marginal-zone lymphomas described in the Revised European–American Lymphoma (REAL) Classification proposed by Harris et al. in 1994 are monoclonal B-cell proliferations considered to represent neoplasms derived from marginal-zone lymphocytes [1–3]. These lymphomas have been subtyped according to anatomic site to include the extranodal mucosa-associated lymphoid tissue (MALT) lymphomas, the nodal monocytoid B-cell (MBCL) lymphomas, and the splenic marginal-zone lymphomas. The marginal zone is a major B-cell region external to the mantle zone that is well defined in the spleen and Peyer's patches but poorly demarcated in peripheral lymph nodes [4]. Marginal-zone lymphocytes are of small size and contain a moderate amount of pale cytoplasm [1]. They appear to have the capacity to mature into both monocytoid B-cells and plasma cells and display tissuespecific homing patterns [1]. As outlined below, distinctive immunohistochemical and cytogenetic features characterize the marginal-zone lymphomas and allow them to be differentiated from mantle-zone and follicular lymphomas. However, the nomenclature and relationships of the marginal-zone lymphoma subtypes require recognition and confirmation by the greater community of pathologists and clinicians.

Pathology
The cytologic features of marginal-zone lymphomas range from the most characteristic small- to medium-sized cells, which have a moderate amount of pale cytoplasm, to small round lymphocytes and to monocytoid B-cells with abundant pale cytoplasm. Typically, nuclear features resemble those of small cleaved cells and are referred to as 'centrocyte-like'. Plasma cell differentiation is found in most specimens, occasional large cells are common [1], and a prominent T-cell component may be present [5]. The lymphoid follicles of marginal-zone lymphomas are reactive; the neoplastic cells occupy the marginal zone and/or interfollicular region [1]. In addition, follicle centers can be selectively replaced by malignant lymphocytes in a pattern that resembles follicular lymphoma, known as 'follicular colonization' [1]. Lymphoepithelial lesions, characterized by infiltration of the epithelium by aggregates of lymphoma cells, are the central feature of the extranodal MALT lymphomas. These lymphoma cells eventually destroy the glandular epithelium. In lymph nodes, the neoplastic cells may have a marginal-zone, parafollicular, or perisinusoidal pattern of distribution [1]. The neoplastic infiltrates in the spleen are found in the marginal zone and in the red pulp [1]. The characteristic histologic features of extranodal and nodal mar-
ginal zone lymphomas are shown in Figure 1 (MALT lymphoma) and Figure 2 (monocytoid B-cell lymphoma).

The immunophenotypic features of marginal-zone lymphoma correspond to the cells of the marginal zone in Peyer's patches [1]. All represent monoclonal B-cell neoplasms that express the pan-B-cell antibodies CD19, CD20, and CD22 and demonstrate light chain restriction. Surface immunoglobulins include IgM, IgG, and IgA (IgM > IgG > IgA) but not IgD. In contrast to other low-grade lymphomas, marginal-zone lymphomas typically express neither the CD5 or CD10 antigens [1]. Recently, trisomy 3 has been demonstrated in about 60% of cases of marginal-zone lymphoma [5]. Recurring abnormalities of chromosome 18 are also seen in marginal-zone lymphoma. Marginal-zone lymphomas characteristically lack rearrangements of the bcl-1 or bcl-2 genes [1].

Clinical features and natural history

Extranodal mucosa-associated lymphoid tissue lymphomas

The MALT lymphoma concept is credited to Isaacson and Wright, who noted that certain low-grade lymphomas of the gastrointestinal tract exhibit features similar to those found in Peyer's patches [6]. In 1983, they proposed that such lymphomas represent the neoplastic counterpart of specialized mucosa-associated lymphoid tissue. Gut-associated lymphoid tissue, which extends from the jejunum to the rectum, is clearly the best characterized and most significant site of MALT. Isaacson and Wright hypothesized that this distinctive lymphoid tissue evolved at permeable mucosal sites in response to direct contact with antigens from the external environment. The low-grade lymphomas known as marginal-zone lymphomas recapitulate the features of this very specialized lymphoid tissue. The MALT lymphoma concept has been extended to the thyroid, salivary gland, lung, ocular adnexa, breast, and other sites [1, 2].

MALT lymphomas arise in sites usually containing no lymphoid tissue, like the stomach and salivary gland, and are associated with Helicobacter pylori infections, autoimmunity, and other chronic inflammatory disorders [1, 2, 5].

Because gastric MALT lymphomas are far more prevalent than those at other sites [1], the clinical features will be described in some detail. Presentation in Western populations is a middle-aged individual with symptoms of nonspecific dyspepsia [3, 7, 8]. Gastritis or peptic ulcer are more common findings than a mass lesion at endoscopy [9, 10]. Staging studies usually demonstrate limited disease, and endoscopic ultrasound may be helpful to determine the extent of involvement. Multifocal involvement remote from the main tumor mass may be seen. The majority of patients are stages I and II, whereas about 20% of patients have proximal node involvement (IIE) [2]. In contrast to other low-grade lymphomas, MALT lymphomas involve the bone marrow in just 5% to 10% of cases. The relationship of gastric MALT lymphoma and Helicobacter pylori is well established.

The bacterium is present in over 90% of cases [2, 9]. In Western populations, lymphoid follicles are found in the stomach only in the presence of chronic gastritis caused by H. pylori. Study of the neoplastic B-cell population by co-culturing with the bacteria demonstrates that it is dependent on T-cells and specific to certain strains of H. pylori. The regression of low-grade gastric lymphoma after eradication of H. pylori was first reported by Wotherspoon et al. in 1993 [9]. Subsequently, multiple case reports and two large series have confirmed these observations [3, 7]. Conclusions from these preliminary data include: 1) H. pylori can be eradicated in nearly 100% of cases, 2) regression of stage IE lymphomas occurs in 60% to 90% of cases [7],
3) resolution of lymphoproliferation may take place over many months after the eradication of bacteria [3], and 4) failure to resolve may indicate the presence of a discordant lymphoma with an intermediate- or high-grade histology.

The clinical behavior of limited-stage MALT lymphoma is so favorable that many, if not most, cases were previously designated 'pseudolymphoma' [2]. Overall 5-year survivals are reported to be 95% or more. Radical surgery is currently being reserved for a minority of gastric MALT lymphomas due to improved histologic recognition from endoscopic biopsies, improved staging with sonoendoscopy, and most importantly, the emergence of eradication of H. pylori as the treatment of choice. The situation is considerably less favorable for the small subset of patients with advanced (III, IV) disease; overall survival at 10 years was only 21% in a recent retrospective series of 19 patients treated with combination chemotherapy in clinical trials conducted by the Southwest Oncology Group as reported by Fisher et al. [11].

MALT lymphomas may involve a variety of other sites: the salivary gland, lung, breast, ocular adnexae, and thyroid are particularly common [1, 2, 12]. In addition to their indolence, remarkable features of these disease sites are the female predominance and age over 50 years [1, 13]. In the case of salivary gland MALT lymphoma, there is often a long-standing history of Sjögren's syndrome or salivary enlargement [14]. Other manifestations of autoimmunity such as rheumatoid arthritis, lupus, or Hashimoto's thyroiditis may be present [1]. Involvement of intraparotid or cervical lymph nodes is usually a late occurrence. Most thyroid lymphomas occur in women over the age of 50 years who have a history of goiter or Hashimoto's thyroiditis [13]. One of the most interesting features of MALT lymphoma is the selective involvement of more than one MALT site, often over a long period of time, in the absence of peripheral lymph node involvement [12]. These clinical observations support preclinical work which indicates selective trafficking of marginal-zone lymphocytes.

The presence of sheets or clusters of transformed cells in the setting of low-grade MALT lymphoma suggests histologic transformation. This can be seen in any of the extranodal sites mentioned, but it is particularly common in the stomach and thyroid [13]. The large-cell lymphoma is presumed to be primary in many cases, since no low-grade component can be detected. In fact, the relationship between low-grade MALT lymphoma and large-cell lymphoma presenting in extranodal sites is not well defined; as many as one third of intermediate-/high-grade gastric lymphomas have a low-grade component when carefully scrutinized.

Nodal monocytoid B-cell lymphoma

Monocytoid B-cell lymphoma (MBCL) is a low-grade lymphoma characterized morphologically by its growth pattern and by its cytomorphology as described above. The close relationship of MALT lymphoma and monocytoid B-cell lymphoma is demonstrated by the fact that lymph nodes secondarily involved by gastric and parotid MALT lymphoma are essentially identical to those of MBCL [14]. In addition, extranodal sites typical of MALT lymphoma are involved in up to one third of MBCL cases. Also, about 25% of MALT lymphomas develop nodal metastases indistinguishable from MBCL [14]. The morphologic features of MBCL resemble hairy-cell leukemia [15], but the two can be distinguished from one another on the basis of disease sites and immunophenotype. MBCL and MALT share the immunophenotypic features discussed in the section on MALT.

Much more commonly than other non-Hodgkin's lymphomas, MBCL presents as a composite lymphoma. These composite lymphomas include follicular, mantle-cell, small lymphocytic, and plasmacytoid lymphomas [15]. Histologic transformation to a diffuse large-cell lymphoma has been reported in several series of MBCL patients. There is a spectrum of B-cell lymphomas seen in conjunction with MBCL; these may be histogenetically related [15].

A marked female predominance characterizes MBCL. The median ages at diagnosis in two studies were 72 years and 65 years [15, 16]. Presenting features include involvement of peripheral lymph nodes in the head and neck region, particularly the paraparotid or intraparotid nodes [15, 16]. The close relationship with MALT lymphoma is exemplified by the involvement of extranodal sites in 9 of 36 cases reviewed at Stanford University, including salivary gland (5 cases), breast, thyroid, stomach, and soft tissue of the chest [16]. The extent of disease at presentation is usually limited; systemic symptoms and bone marrow involvement were rare. Autoimmune disease, especially Sjögren's syndrome, has been a prominent feature in several series [1, 16]. Ten of the 36 Stanford cases had composite or discordant lymphomas; 2 of these were Hodgkin's disease. Transformation to a higher-grade lymphoma occurred in 7 cases. MBCL follows an indolent course. Ten-year survival was 53% in the retrospective series of advanced stage cases from SWOG discussed above, significantly more favorable than MALT lymphoma [11]. However, composite presentations and histologic transformation must be considered in the management of MBCL.

**Splenic marginal zone lymphoma**

Splenic marginal-zone lymphoma (SMZL) has been described by Schmid et al. as a primary splenic lymphoma arising in the marginal zone [4]. The histologic features include follicular colonization and infiltration into the red pulp, in addition to the marginal-zone pattern [4, 17]. Primary splenic lymphomas of any histologic subtype are uncommon, representing no more than 3% of the non-Hodgkin's lymphomas. They are
typically widespread low-grade B-cell neoplasms that are considered to be related to different splenic compartments. The classification of splenic lymphomas, however, has remained somewhat controversial [18].

In a series of 13 cases of SMZL, 12 were found to have bone marrow involvement and peripheral blood lymphocytosis was noted in 11 by morphologic and flow cytometric analyses [18]. Adjacent nodal involvement was indistinguishable from MBCL. As with other marginal-zone lymphomas, these cases had a low proliferative rate. Despite the extent of disease, the cases followed an indolent, protracted course [18]. The relationship between SMZL and a condition known as splenic lymphoma with villous lymphocytes, which can be confused with hairy-cell leukemia [19], requires further study [18]. However, Isaacson et al. have recently reported that the histopathology of splenic lymphoma with villous lymphocytes is indistinguishable from that of SMZL [19]. A comparison of these subtypes can be found in Table 1.

Treatment

The treatment results for marginal-zone lymphoma are difficult to summarize because these lymphomas represent only 1% to 5% of nodal and <1% of splenic and bone marrow B-cell neoplasms [20]. Furthermore, as they have been recognized only rather recently, they have been commonly misclassified, particularly in the Working Formulation, as diffuse small cleaved cell, follicular low-grade, or small lymphocytic lymphomas [11]. Among a group of 1091 nonfollicular lymphomas seen in the Centre Hospitalier Lyon-Sud, there were 43 MALT lymphomas, 3 MBCL, and 3 SLVLs [10]. In this series, the time to treatment failure with diverse therapeutic approaches was only 48 months with no evidence of a cured population. Similarly, the survival plots in the series of patients treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy reported by Fisher et al. demonstrated an indolent natural history with the inexorable relapse rate typical of low-grade lymphoma [11].

Because the MALT lymphomas typically present with limited disease, local therapies may be considered. Gastrectomy, as noted above, is currently not favored for gastric MALT lymphoma because of the long-term consequences of surgery and the efficacy of antibiotics. The role of radiation therapy for localized disease should not be forgotten. Because splenic lymphomas frequently present with flank pain and no obvious peripheral adenopathy, splenectomy has frequently been performed for diagnostic and therapeutic purposes [18]. This has resulted in durable palliation despite the presence of more extensive disease in the bone marrow. The efficacy of single-alkylating-agent chemotherapy, cyclophosphamide or chlorambucil, in 24 patients with gastric MALT lymphoma was summarized by Hammel et al. [21]. A 75% complete response rate was found in 17 patients with stage IE and 7 patients with stage IV disease. The median time to treatment failure was 58 months with no indication of cure. An international study has been initiated to compare antibiotic therapy alone or in combination with chemotherapy for the treatment of gastric MALT lymphoma.

Role of purine analogs

The purine analogs 2-chlorodeoxyadenosine and fludarabine have demonstrated single-agent efficacy in previously treated and untreated indolent non-Hodgkin's lymphomas [22–30]. Given the relatively high response rates, including complete responses, these drugs are being investigated as primary therapy for low-grade lymphoma. Combination therapy with alkylating agents and mitoxantrone has also been assessed in previously treated patients and, more recently, as initial treatment [31, 32]. The early studies of previously treated low-grade lymphoma include very few patients with marginal-zone lymphoma. However, it is probable that some patients with these lymphomas were treated but were classified incorrectly. For instance, in the report of 2-chlorodeoxyadenosine (2-CdA) as an active salvage agent in advanced indolent non-Hodgkin's lymphoma, a significant proportion of patients were considered to have diffuse small cleaved-cell lymphoma, a subtype which is not recognized in the REAL Classification [1, 27]. Among 28 previously untreated patients, Saven et al. reported one case each with MALT lymphoma and MBCL [30]. Both responded to 2-CdA, one with a complete and the other with a partial response.

The theoretical basis for the use of the purine analogs in the marginal-zone lymphomas is based on the specificity of these drugs for lymphoid cells and the low proliferative rate of these low-grade lymphomas. In contrast to traditional antimetabolites, for instance, 2-CdA is equally active against both resting and dividing cells [33]. Preclinical studies indicate that the purine analogs induce apoptosis, a physiologic mechanism of cell death [34]. On this basis, the purine analogs may be considered for the treatment of the marginal-zone lymphomas as second-line therapy after alkylating agents. Because of the unique mechanism of action of these agents, combination therapy for untreated patients is reasonable in the context of a clinical trial. The development of oral formulations should facilitate drug delivery and make the purine analogs more attractive therapeutic agents for low-grade lymphomas, including the marginal-zone lymphomas.
Table 1. Characteristics of marginal-zone lymphoma subtypes.

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<tr>
<th>Subtypes</th>
<th>Rappaport</th>
<th>Kiel</th>
<th>WF</th>
<th>Morphology</th>
<th>Immunophenotype</th>
<th>Genetic features</th>
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<th>Postulated normal counterpart</th>
<th>Survival</th>
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<td>Extra-nodal</td>
<td>Well-differentiated</td>
<td>Monocytoid A, B, C*</td>
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<td>Varied cytology</td>
<td>IgM &gt; IgG &gt; IgA</td>
<td>Trisomy 3</td>
<td>Adults, age &gt; 50</td>
<td>Marginal zone B-cell</td>
<td>Limited stage 95% 5 years [2]</td>
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<td>lymphocytic</td>
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<td>'Centrocyte-like'</td>
<td>IgD⁺</td>
<td>Abnormalities chromosome 18 t(11;14)⁻ t(14;18)⁻</td>
<td>Site-specific symptoms</td>
<td>Stage III, IV 21% 10 years [11]</td>
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<td>Plasma cell differentiation</td>
<td>CD19⁺, 20⁺, 22⁺ CD43⁺, CD11c⁺ CD5⁺, CD10⁺, CD23⁺</td>
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<td>Cytologic features as above</td>
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<td>Female predominance</td>
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<td>Monocytoid B-cell lymphoma</td>
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<td>Monocytoid B-cells with abundant pale cytoplasm</td>
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<td>Perisinusoidal, parafollicular or marginal zone distribution</td>
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<td>Significant proportion have extranodal disease</td>
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<td>Splenic</td>
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<td>Marginal zone proliferation with infiltration of red pulp</td>
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<td>Indolent natural history</td>
<td>Splenic marginal zone B-cell</td>
<td>Relatively long survival</td>
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* A = small lymphocytic; B = follicular small cleaved cell; C = follicular mixed small cleaved and large cell.
References


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