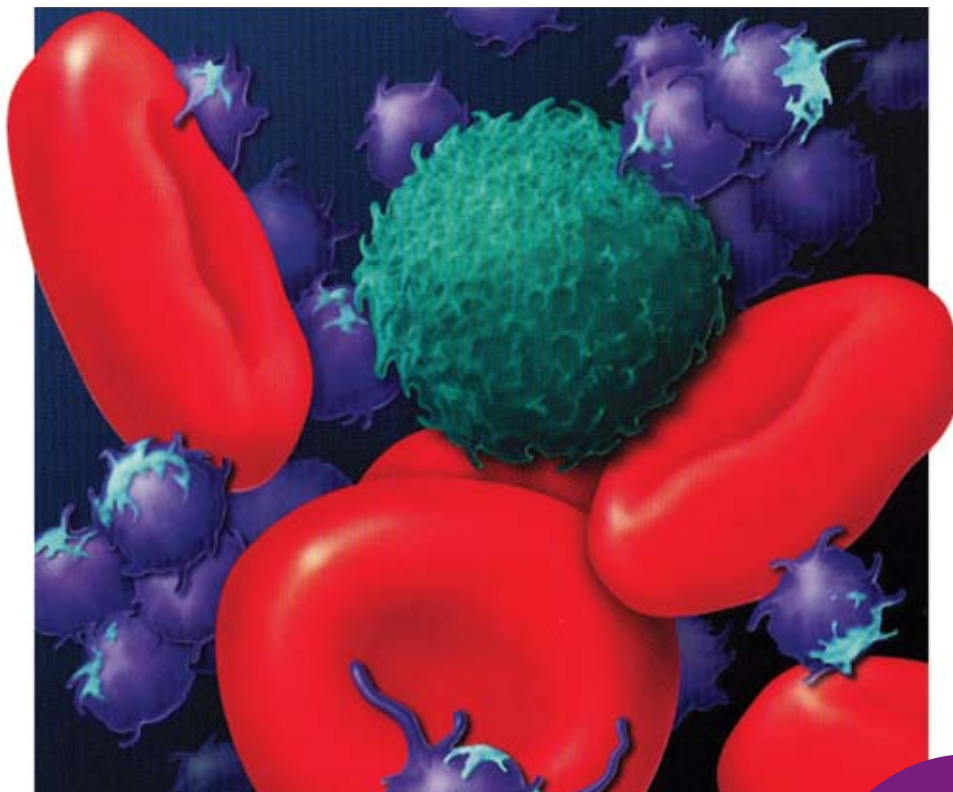


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Indolent B-Cell Non-Hodgkin Lymphoma

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HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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Indolent B-Cell Non-Hodgkin Lymphoma

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Indolent B-Cell Non-Hodgkin Lymphoma

Robert Frank Cornell, MD, and Timothy S. Fenske, MD

INTRODUCTION AND CLASSIFICATION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders that involve neoplastic expansions of B cells, T cells, NK cells, or histiocytic/dendritic cells. Each has distinctive biological and clinical manifestations, making accurate diagnosis essential to management. Indolent lymphomas are generally considered incurable; however, with recent improvements in treatment, patients are living longer and often with preserved quality of life. The median survival was historically around 8 to 10 years; however, this likely represents an underestimation for patients diagnosed currently in the setting of improved treatment options. Patients may be asymptomatic for years prior to requiring treatment.

Indolent B-cell NHLs are best classified by correlation of morphologic, immunophenotypic, cytogenetic, and clinical features. An adequate tissue sample is vital to diagnosis and generally is best obtained by an excisional lymph node biopsy. The key characteristics are shown in **Table 1**. The current classification system is the 2008 World Health Organization (WHO) system.¹

EPIDEMIOLOGY

NHL represents the sixth most common malignancy in both men and women annually in the United States. Over 65,000 new cases of NHL were diagnosed in 2010, and of these approximately 36% were indolent NHL.^{2,3} Over the past 30 years the overall incidence of NHL has been increasing around 2% to 3% per year in the Western world. In most cases the etiology for indolent NHL is unknown; however, associations have been made between indolent NHL and certain autoimmune disorders, immunodeficiency states, and infectious agents. One example is gastric MALT (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue) lymphoma, which is strongly associated with *Helicobacter pylori* infection.

STAGING AND WORKUP

Following diagnosis, baseline complete blood count with differential, lactate dehydrogenase, chemistry panel, liver function tests, and β_2 -microglobulin are routinely obtained. Viral serological testing, including HIV and hepatitis B and C, should also be obtained. Imaging with a computed tomography (CT) scan of the neck, chest, abdomen and pelvis is important for staging. Positron emission tomography (PET) can be useful in staging and assessing response in some cases of indolent B-cell NHL, although according to the International Working Group criteria, PET scan is not routinely recommended.⁴ Bone marrow biopsy and aspirate should be obtained for staging of most patients. The Ann Arbor staging system is used for NHL (**Table 2**).⁵ Based on the treatment plan, baseline evaluation of cardiac and pulmonary function may be indicated.

INDOLENT B-CELL NHL SUBTYPES

FOLLICULAR LYMPHOMA

Follicular lymphoma (FL) is the most common indolent B-cell lymphoma, representing 20% of lymphomas in the United States and Europe. The median age at diagnosis is 59 years with a male-to-female ratio of 1:1.7.⁶ There are approximately 11,000 new cases per year in the United States, with an annual incidence of 3.2 cases per 100,000 persons per year. FL is more common in Caucasians compared to other ethnic groups.⁷ Treatment options and efficacy have improved significantly since the late 1990s with the introduction of the anti-CD20 monoclonal antibody rituximab, radioimmunotherapy, other novel agents, and a more effective use of stem cell transplantation.

FLs originate from germinal center B cells. The tumor demonstrates a follicular pattern of growth and is composed of small cleaved cells (centrocytes) and large cells (centroblasts). Nearly all cases of FL express the pan-B-cell antigens CD19, CD20, and CD79a. CD10

Table 1. Immunophenotypic and Cytogenetic Features of Indolent B-Cell Non-Hodgkin Lymphomas (NHL)

NHL*	CD5	CD10	CD20	CD23	Cytogenetics	Oncogene
FL	–	+	+	–/+	t(14;18)	<i>BCL2</i>
MZL	–	–	+	–	t(11;18), t(1;14)	<i>cIAP2-MALT1, BCL10</i>
SLL	+	–	Weak	+	13q del, 11q del, trisomy 12, 17p del	
LPL	–	–	+	–	t(9;14)†	
SMZL	–	–	+	–	7q32 del (40%)	

*All listed NHLs are positive for pan-B-markers CD19, CD22, and CD79a.

†t(9;14) specific for LPL is controversial (see text for details).

FL = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma; SMZL = splenic marginal zone lymphoma.

is expressed in 60% of cases.^{1,8} In approximately 85% of cases, there is strong cytoplasmic staining of the *BCL2* protein.⁹ CD21 is typically positive, highlighting follicular dendritic cell networks. The key cytogenetic feature, present in 85% of FL cases, is the translocation t(14;18)(q32;q21), which results in an *IgH/BCL2* fusion gene, overexpression of the *BCL2* oncogene, and an anti-apoptotic effect.^{10,11}

FL is assigned a grade from 1 to 3 according to the number of centroblasts seen per high-power field (hpf).^{1,12} Grade 1 is defined as 0 to 5 centroblasts/hpf, grade 2 as 6 to 15 centroblasts/hpf, and grade 3 as more than 15 centroblasts/hpf. Grade 3 is divided into 3A and 3B, with 3B containing solid sheets of centroblasts. Some studies suggest that grade 3 FL behaves clinically in a manner akin to an aggressive lymphoma, with the potential for long-term remission following anthracycline-based therapy.^{13,14} Other studies have shown that the outcomes with grade 3 FL do not differ significantly from grade 1 to 2 FL, with the possibility of deferred initial therapy and with nearly all patients eventually relapsing.^{15–17} The outcomes for patients with grade 3A versus 3B FL do not appear to differ significantly.^{13,17}

Presentation and Prognostic Features

Patients with FL most commonly present with multiple sites of slowly progressive painless lymphadenopathy. Enlarged lymph nodes can wax and wane. About two-thirds of patients present with stage III or IV disease. Approximately 30% of patients present with “B” symptoms. About 60% to 70% of patients have bone marrow involvement at diagnosis, with the typical pattern consisting of paratrabecular lymphoid aggregates.

Historically the median overall survival for FL patients was in the range of 8 to 10 years, with no significant improvement in outcomes from the 1960s through the early 1990s.¹⁸ However, since the introduction of

rituximab, overall survival has clearly improved.¹⁹ While FL is still generally considered incurable, some patients do achieve remissions lasting 10 years or longer.

Prognosis for an individual patient can be assessed using the Follicular Lymphoma International Prognosis Index (FLIPI) score (Table 3). Overall survival is based on the number of risk factors present, with 10-year survival ranging from 35% to 71%.²⁰ More recently the FLIPI2 score was developed using patients treated in the rituximab era. The FLIPI2 score can separate patients into groups with 3-year progression-free survival (PFS) ranging from 51% to 91%.²¹ Gene expression profiling has also been shown to predict survival.²² In addition, a low lymphocyte-associated macrophage content has been associated with improved overall survival.²³

Histologic transformation into an aggressive lymphoma, usually diffuse large B-cell lymphoma (DLBCL), occurs at a rate of approximately 20% to 30% at 8 to 10 years, or approximately 3% per year.²⁴ Transformation carries a poor prognosis, with median survival of about 1.5 years; however, patients not previously treated have a better prognosis.²⁵ It is generally characterized by rapid growth of lymph nodes along with worsening or new B symptoms. Occasionally, FL transforms into Burkitt lymphoma^{26,27} or precursor B-lymphoblastic lymphoma/acute lymphocytic leukemia.²⁸

Treatment

FL generally follows an indolent disease course. Patients may live for many years without treatment. In fact, some patients experience a waxing and waning course, with up to 23% achieving spontaneous remission for 5 years or longer before treatment.^{29,30} A watch-and-wait approach is appropriate in asymptomatic patients with low disease burden, such as those with no site of disease measuring 7 cm or larger and no more than 3 sites of disease between 3 and 7 cm.

Table 2. Ann Arbor Staging System

Stage I	Involvement of a single lymph node (LN) region (I) or single extralymphatic organ or site (IE)*
Stage II	Two or more LN regions on the same side of the diaphragm (II) or single extranodal site with involvement of limited, contiguous adjacent organ or tissue (IIE)
Stage III	LN involvement on both sides of the diaphragm (III). This may include the spleen (IIIS), extralymphatic tissue (IIIE), or both (IIISE). [†]
Stage IV	Disseminated involvement of one or more extralymphatic organs (eg, bone marrow, liver)

*Each stage is subdivided into “A” and “B” based on the absence or presence of “B” symptoms, respectively. B symptoms include unexplained fevers, weight loss of 10% or more of body weight over 6 months, and/or night sweats.

[†]The suffix “X” can be applied to bulky disease (>10 cm maximum dimension).

Adapted from Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin’s disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630–6.

Patients need to be assessed at diagnosis and at regular intervals to determine whether treatment is indicated. Indications for treatment include high disease burden, symptoms from bulky disease, symptomatic extranodal disease, B symptoms, progressive disease over 6 months, histological transformation, massive or symptomatic splenomegaly, and cytopenias from extensive bone marrow involvement.

For patients with stage I or II FL, locoregional radiation therapy has commonly been recommended. Such treatment results in a long-term disease-free survival (DFS) rate of around 40% to 50% at 10 years.^{31–33} Since most patients go on to recur eventually (and generally outside of the radiation field), it does not appear that locoregional radiation therapy alters the natural history of the disease. As a result, some experts advise against radiation therapy in this setting, and the optimal treatment for limited-stage FL remains controversial. The addition of chemotherapy to radiation has not been shown to improve overall survival but has been shown to reduce relapse rates.^{34,35} It is unknown if administering rituximab in conjunction with locoregional radiation improves outcomes further.

Most patients with FL present with stage III or IV disease. In such patients, the addition of rituximab to various combination chemotherapy regimens has been shown to improve PFS and (in most studies) overall survival in patients with FL, compared to chemotherapy alone.^{36–38} Therefore, inclusion of rituximab with frontline chemotherapy is now considered a standard of care. In the United States, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has been the most commonly used initial treatment for FL.³⁹ R-CVP (rituximab, cyclophosphamide, doxorubicin, and vincristine) is also frequently used. This regimen is somewhat less active than R-CHOP, but also less toxic.³⁶ Recently, bendamustine plus rituximab has become a popular frontline regimen based on recent unpublished

data showing superiority to R-CHOP, with improved efficacy and a more favorable toxicity profile.⁴⁰

Single-agent rituximab has also been studied, with early data showing high response rates and a low toxicity profile.^{41–43} However, long-term data is not yet available, and these studies have used various dosing schemes. In general, single-agent rituximab is considered a reasonable treatment option for patients with a low disease burden and minimal disease-related symptoms.

Following first-line chemoimmunotherapy, patients may undergo observation, “maintenance” rituximab, or consolidation with radioimmunotherapy (RIT). The use of rituximab as a maintenance therapy has gained popularity in recent years. The PRIMA trial evaluated the impact of maintenance rituximab following frontline rituximab/chemotherapy treatment. This phase III randomized study showed a 3-year PFS in favor of maintenance rituximab. So far, no difference in overall survival is apparent between the groups.⁴⁴ Other studies in the frontline setting have shown a benefit to maintenance rituximab following rituximab induction⁴⁵ or after CVP (cyclophosphamide, vincristine, and prednisone) induction.⁴⁶ ⁹⁰Y-ibritumomab tiuxetan (a radioimmunoconjugate) was studied as consolidation therapy after frontline chemotherapy (± rituximab). Patients who received RIT as consolidation demonstrated significantly improved PFS compared to those simply observed after frontline therapy. However, interpretation of this data is limited by the fact that the majority of patients did not receive rituximab with induction therapy.⁴⁷

There are many potential treatment options to consider with recurrent FL. When possible, patients should be enrolled in a clinical trial. Off-protocol options include (1) single-agent rituximab with or without maintenance rituximab; (2) various chemotherapy regimens (± rituximab) including bendamustine, CHOP, chlorambucil, fludarabine, or platinum-based regimens;

Table 3. Follicular Lymphoma International Prognostic Indices

FLIPI			FLIPI2		
Age > 60 yr			Age > 60 yr		
Hemoglobin < 12 g/dL			Hemoglobin < 12 g/dL		
Stage III or IV disease			Bone marrow involvement		
LDH > ULN			B2M > ULN		
Greater than 4 nodal sites			Largest nodal diameter >6 cm		
Score (risk)	5-year OS (%)	10-yr OS (%)	Score (risk)	3-yr PFS (%)	3-yr OS (%)
0–1 (low)	91	71	0 (low)	91	99
2 (intermediate)	78	51	1–2 (intermediate)	69	96
≥3 (high)	52	36	≥3 (high)	51	84

B2M = β_2 -microglobulin; LDH = lactate dehydrogenase; OS= overall survival; PFS = progression-free survival; ULN = upper limit of normal.

Adapted from Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood* 2004;104:1258–65; and Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol* 2009;27:4555–62.

(3) radioimmunotherapy; (4) external-beam radiation; (5) hematopoietic stem cell transplant (autologous or allogeneic); or (6) novel biological agents such as bortezomib, lenalidomide, or novel monoclonal antibody therapies.⁴⁸ In general, FL is characterized by progressively shorter remissions with each relapse. Factors to consider when selecting treatment include previously used treatments (and response to those), number of relapses, and patient factors including symptoms, age, tumor burden, comorbidities, and frailty. It is also important to consider the patient’s goals of therapy, willingness to accept risk, and psychosocial situation in selecting the optimal therapy.

MARGINAL ZONE LYMPHOMA

Marginal zone lymphoma (MZL) represents a group of distinct indolent NHLs including extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal marginal zone lymphoma, and splenic marginal zone lymphoma. These arise from the post-germinal center marginal zone of B-cell follicles. Such follicles reside in mucosal, spleen, and lymph node tissue. MZL is the third most common subtype of NHL after DLBCL and FL, accounting for 5% to 10% of NHL. Of this, MALT lymphoma is the most common form, representing 70% to 80% of MZL.¹

MALT Lymphoma

MALT lymphoma (or “MALToma”) arises from epithelial surfaces and is associated with sites of chronic inflammation. It most commonly presents as localized disease, displays an indolent clinical behavior, and carries a very good long-term prognosis. About 30% of

MALT lymphomas arise from the gastric mucosa, with the remaining cases arising from nongastric sites. In most cases, gastric MALT lymphoma is associated with *H. pylori* infection.^{49,50}

A key histologic feature of MALT lymphoma is the presence of lymphoepithelial lesions. In some cases plasma cells (or “plasmacytoid differentiation”) are seen. Immunohistochemistry for MALT lymphoma has no characteristic marker. A key point for diagnosis is the lack of staining with CD5, CD10, CD23, and cyclin D1 (Table 1). These markers (along with the histology and cytogenetic studies) allow for the exclusion of FL, mantle cell lymphoma, and small lymphocytic lymphoma. The most common translocation in MALT lymphoma is t(11;18)(q21;q21), present in 15% to 40% of cases.^{51,52} This translocation yields a fusion between the *MALT1* gene from 18q21 with the cellular inhibitor of apoptosis inhibitor-2 (*cIAP2*) gene from 11q21, resulting in the *cIAP2-MALT1* fusion.

The clinical presentation of MALT lymphoma depends on the primary site involved. The most common site of involvement is the stomach, with the majority of patients presenting with localized disease. Patients may present with epigastric pain, nausea, dyspepsia, reflux, weight loss, and iron deficiency anemia from gastrointestinal tract blood loss. “B” symptoms are uncommon. The majority of gastric MALT lymphomas are secondary to *H. pylori* infection.^{50,53} About two-thirds of gastric MALT lymphomas regress with treatment of *H. pylori* infection with antibiotics and proton pump inhibitors.^{54,55} Diagnosis can be achieved via esophago-gastroduodenoscopy (EGD) to sample the gastric wall, along with endoscopic ultrasound, which allows for

sampling of perigastric lymph nodes. Multiple biopsies from each region should be obtained. *H. pylori* testing by biopsy should be performed. If negative, it is recommended that serologic testing be performed.⁵⁶ Bone marrow biopsy is recommended, although it is positive in only approximately 15% of cases.^{55,57} CT of the chest, abdomen, and pelvis is recommended to evaluate for other sites of disease.

Treatment of localized gastric MALT lymphoma is best achieved by *H. pylori* eradication using “triple therapy” consisting of a proton pump inhibitor plus antibiotics. Multiple regimens exist and antibiotic choice should be guided based on regional antibiotic resistance patterns. Should first-line treatment fail, bismuth-containing “quadruple therapy” may be effective.⁵⁸ In patients with early stage, *H. pylori*-proven disease without t(11;18), complete remission occurs in about 75% of cases.^{59,60} Patients with t(11;18) are less likely to respond to *H. pylori* treatment.⁶¹ *H. pylori* eradication should be proven via follow-up EGD with biopsies. In cases of remission, continued surveillance with EGD and biopsies should be performed to monitor for recurrence. Regression of lymphoma can be slow after *H. pylori* eradication, in some cases taking longer than 1 year.⁶² Patients with gastric MALT lymphoma overall have better outcome compared to disease originating at other extranodal sites.⁶³

For patients with localized disease who are *H. pylori* negative or who fail to respond to *H. pylori* treatment, treatment with radiation therapy results in complete remission in over 90% of cases and is considered by most to be the standard treatment in this setting.^{64,65} Surgery has not been shown to be superior to other treatment approaches and is not recommended.⁶⁶ In patients with advanced disease and those unable to receive radiation therapy, the decision to treat is based on patient symptoms, comorbidities, progression, tumor burden, and disease status. Since MALT lymphoma is an indolent lymphoma, a watch-and-wait approach may be appropriate. In patients with symptomatic disease, systemic treatment similar to that used for FL is used. In a small study of gastric MALT lymphoma, use of rituximab alone resulted in a response in 77% of patients.⁶⁷

Nongastric extranodal MZL accounts for two-thirds of MALT lymphoma and can occur in numerous sites including skin, head and neck, breast, orbits, salivary glands, lung, thyroid, bladder, small intestine, pancreas, and others.⁶⁸ There are some reports of associated infections including *Chlamydia psittaci* with ocular adnexal MZL, *Borrelia burgdorferi* with cutaneous MZL, and *Campylobacter jejuni* with immunoproliferative small intestinal disease in the Middle East.⁶⁹⁻⁷¹ In addition, there is increased risk of nongastric extranodal MZL

in patients with chronic autoimmune conditions such as Sjögren syndrome.⁷² Disseminated disease is more common in nongastric MZL than in the gastric form, occurring in about 25% of nongastric MZL patients.⁵⁷ Despite this, the 5-year overall survival is approximately 90%.⁶⁸ Localized disease can be managed with radiation therapy alone.⁷³ For patients with advanced stage disease, a treatment approach similar to that used in advanced stage FL is recommended.

Nodal Marginal Zone Lymphoma

Nodal marginal zone lymphoma (NMZL) is a rare lymphoma subtype accounting for 1.5% to 1.8% of NHL cases.^{1,74} The histologic and immunophenotypic features resemble extranodal and splenic lymphoma without evidence of disease involvement at those sites. CD38 and MUM1 can be positive and are associated with plasmacytic histology.⁷⁵ No consistent identifiable cytogenetic abnormality has been identified. The t(11;18)(q21;q21) translocation associated with MALT lymphoma is not found with NMZL.⁷⁶

The median age of presentation is between 50 and 60 with a slight male predominance. The majority of cases present with advanced stage disease. Peripheral and abdominal lymph nodes are most commonly involved. Patients uncommonly have B symptoms or peripheral blood involvement. Bone marrow involvement occurs in about 30% to 40% of cases. An association with hepatitis C is seen in about 20% of cases. Approximately 10% of patients have a small to moderate IgM paraprotein.^{74,77-79}

Due to the rarity of this disorder, specific prognostic factors are largely unknown. In one study, a higher FLIPI score correlated with a worse prognosis.⁷⁷ The 5-year survival ranges between 55% and 79% at 5 years.^{6,74,75,80} Complete response with initial treatment occurs in 50% to 60% of patients. Transformation to DLBCL has been reported, with 16% transformed at a median time of 4.5 years from diagnosis.⁷⁴

No prospective trials are available to establish a standard of care for NMZL. In addition, there is no data published regarding outcome with use of rituximab. Most clinicians use a therapeutic approach to NMZL that mirrors the approach used for FL. In patients with localized disease, radiation therapy can achieve good tumor control.^{75,78,79} In cases with low-tumor burden, an active surveillance strategy can be used. Alternatively, single-agent rituximab may be effective. In symptomatic patients or those with high-tumor burden, combination chemotherapy with rituximab should be given. Autologous or allogeneic transplantation can be considered for younger patients with relapsed disease or histologic transformation.⁸¹

Splenic Marginal Zone Lymphoma

Splenic marginal zone lymphoma (SMZL) is a rare form of MZL that represents less than 1% of all NHL. Patients typically present with splenomegaly, which can be massive, as well as cytopenias. Median age at diagnosis is around 60 years.⁸² Over 90% of cases will have bone marrow or peripheral blood involvement.^{83,84} Patients often present with symptoms from cytopenias including anemia and thrombocytopenia. The low blood counts are primarily secondary to splenic sequestration as opposed to extensive bone marrow infiltration. Peripheral lymph node involvement is uncommon. About one-third of patients have a monoclonal gammopathy, usually IgM.^{85,86} SMZL is associated with autoimmune conditions including autoimmune hemolytic anemia in 10% to 15% of patients, and rarely with immune thrombocytopenia, cold agglutinin disease, lupus anticoagulant, and neuropathies.⁸⁷ An association between hepatitis C infection and SMZL has been described.^{88,89}

Given the indolent nature of SMZL, most patients have stage IV disease by the time of diagnosis. Diagnosis can often be achieved by bone marrow and peripheral blood analysis. In some cases, splenectomy may be required to determine diagnosis. SMZL generally has a favorable prognosis, with a median overall survival between 5 and 15 years.^{83,86,90} Peripheral node involvement is associated with a poorer prognosis.⁷⁴ About 15% of SMZL cases ultimately transform into large cell lymphoma.^{91,92}

Morphologically, small B-lymphocytes are seen. Peripheral blood lymphocytes may display villous projections, which led to the now outdated term “splenic lymphoma with villous lymphocytes” in reference to SMZL.^{93,94} The immunophenotype with SMZL is similar to NMZL and MALT lymphoma.⁸² Lack of CD25 and CD103 help distinguish SMZL from hairy cell leukemia. Chromosomal changes, often complex, are common in SMZL and present in about 80% of cases. In 40% of cases there is a deletion or translocation of 7q32.^{95,96} As with NMZL, the MALT-associated t(11;18)(q21;q21) translocation is not seen in SMZL.

Given the indolent nature of SMZL, active surveillance is appropriate in asymptomatic patients.^{85,86} In patients with massive splenomegaly or severe cytopenias, splenectomy is an effective first-line treatment that allows for rapid improvement of the cytopenias and symptoms.^{85,97} For patients unable to undergo surgery or for whom a rapid response is not necessary, rituximab, a rituximab/chemotherapy combination, or splenic irradiation are options.^{98–102} For patients with extensive bone marrow involvement or other significant extrasplenic disease burden, rituximab with or without chemotherapy should be

considered. Limited data exists to determine the superiority of one particular chemotherapy regimen. Other regimens used to treat indolent lymphomas, combined with rituximab, are often applied. One study showed an excellent response to single-agent rituximab or rituximab/chemotherapy combinations, with response rates of over 80% to single-agent rituximab.¹⁰¹ It is clear that rituximab is highly active in SMZL and unclear whether chemotherapy adds significant benefit to rituximab alone. In cases of SMZL for which an immediate response is not required, it is therefore reasonable to use single-agent rituximab as the initial therapy. For patients with SMZL associated with hepatitis C, antiviral therapy may produce a complete clinical regression of SMZL.¹⁰³

SMALL LYMPHOCYTIC LYMPHOMA

The WHO classifies chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) as biologically the same condition with different manifestations. CLL involves the bone marrow and peripheral blood, while SLL has a primarily nodal presentation, without a leukemic phase. CLL/SLL is a B-cell neoplasm of the elderly, with a median age of 65 years at diagnosis.⁶⁶ SLL accounts for 6.7% of NHL.¹⁰⁴ Only 5% to 10% of patients with CLL/SLL lack a leukemic phase and therefore meet criteria for SLL.

Diagnosis of SLL is typically made via lymph node biopsy. In SLL, the peripheral blood absolute lymphocyte count (ALC) will be less than 5000/ μ L, while in CLL the ALC will be greater than 5000/ μ L for more than 3 months. Characteristic immunophenotypic findings for CLL/SLL include expression of CD5, CD19, CD20, and CD23. Expression of CD20 is dim, and occasionally CD23 is absent. One key feature is dim expression of surface immunoglobulin. CD38 is expressed in 40% of cases, with high expression of CD38 associated with an adverse prognosis.¹⁰⁵

Patients with SLL often present with generalized painless adenopathy. About one-quarter have B symptoms.⁶ Spleen or liver involvement may be present, along with other sites of extranodal disease. Approximately 4% to 10% of patients with CLL/SLL will also have autoimmune hemolytic anemia,^{106,107} with 2% to 3% manifesting immune thrombocytopenia and rarely pure red cell aplasia.¹⁰⁸ Patients may also present with bacterial infection due to hypogammaglobulinemia, which can be managed with immunoglobulin replacement.

The Rai and Binet systems are used for CLL staging,^{109,110} but because SLL is considered a lymphoma, the Ann Arbor staging system is more commonly used. In addition to clinical stage, cytogenetic abnormalities are important in determining prognosis. As in CLL, the

most common cytogenetic abnormalities are deletion 13q, deletion 11q, trisomy 12, and deletion 17p. Most studies have evaluated these cytogenetic abnormalities in the context of CLL rather than SLL alone. However, some studies have shown these abnormalities to be present in both SLL and CLL. A recent study showed no statistical difference between SLL and CLL in terms of the frequency of specific cytogenetic abnormalities or IgVH mutational status.^{111,112} While there is limited data regarding prognosis for specific cytogenetic abnormalities in SLL, this has been widely studied for CLL, with deletions of 17p and 11q and unmutated IgVH associated with poor prognosis.¹¹³ As with other indolent lymphomas, transformation of CLL/SLL into a more aggressive histology can occur. The transformed histology is most frequently DLBCL and less commonly prolymphocytoid leukemia, Hodgkin lymphoma, or acute myeloid leukemia. Patients typically present with worsening B symptoms, enlarging and bulky adenopathy, and cytopenias. Transformation has an incidence between 2% and 8%, with median survival between 5 and 19 months after transformation.¹¹⁴

A number of factors should be considered regarding treatment of SLL. It is generally an indolent condition, and active surveillance is a reasonable approach in asymptomatic patients. Delayed treatment compared to immediate chemotherapy with use of alkylating agents has shown no survival benefit for CLL/SLL.¹¹⁵ In addition, CLL/SLL is not considered curable (with the possible exception of patients undergoing allogeneic stem cell transplantation) and therefore treatment is usually aimed at controlling the disease for as long as possible. Indications for treatment include severe B symptoms, bulky symptomatic adenopathy, recurrent infections, significant cytopenias, autoimmune phenomena, and lymphocyte doubling time less than 6 months.¹¹⁶ Patients appropriate for watch-and-wait should have blood counts and a physical exam every 3 to 6 months. Some patients can be observed for 5 or more years before requiring treatment. First-line chemotherapy is not standardized for SLL. By extrapolation from CLL, fludarabine-based chemotherapy can be utilized. One can also treat SLL using FL regimens, although there is relatively little data evaluating these regimens specifically in SLL.

For patients with relapsed or refractory CLL/SLL, depending on prior therapy received, treatment options include bendamustine, platinum-based lymphoma salvage regimens, or fludarabine-based regimens. Alemtuzumab, an anti-CD52 monoclonal antibody, has significant activity in CLL but is much less active for nodal disease, and is therefore not commonly used

in SLL. Ofatumumab, a fully humanized anti-CD20 antibody with greater affinity for CD20 than rituximab, is indicated for CLL/SLL which has failed fludarabine and alemtuzumab therapy; it also has activity in relapsed low-grade NHL.¹¹⁷ For relapsed SLL patients with chemosensitive disease, high-dose chemotherapy and autologous stem cell transplantation can be considered. Younger patients without significant comorbidities can also be considered for allogeneic stem cell transplantation, which can result in long-term remissions in some patients.^{118,119}

LYMPHOPLASMACYTIC LYMPHOMA

Lymphoplasmacytic lymphoma (LPL) is an uncommon indolent B-cell neoplasm accounting for approximately 1% of all hematologic malignancies in the United States and Western Europe, and less than 5% of all NHL.^{6,7,104} Waldenström macroglobulinemia (WM) is found to frequently coexist with LPL and is defined by the presence of an IgM monoclonal gammopathy and lymphoplasmacytic bone marrow involvement. The median age of diagnosis is around 65 years. LPL is not considered curable, and the median survival is 5 to 10 years.¹²⁰

LPL is usually sporadic, but there are reports of familial involvement.¹²¹ Patients with LPL present with symptoms based on sites of involvement including adenopathy, organomegaly, B symptoms, and cytopenias. In the case of WM, patients may present with symptoms related to monoclonal protein production such as hyperviscosity, neuropathy, cryoglobulinemia, or cold agglutinin disease. In addition, hepatitis C is associated with LPL and mixed cryoglobulinemia.¹²² Hyperviscosity syndrome occurs in about 20% of WM cases.^{120,123} Symptoms of hyperviscosity typically occur when the serum viscosity is greater than 4.0 centipoises (cp) or the monoclonal IgM level is greater than 4 to 5 g/dL. Clinical manifestations include bleeding, neurological symptoms (such as headache, delirium, ataxia, or coma), and visual disturbances from retinal hemorrhage or thrombosis. Hyperviscosity can cause sludging and dilation in the retinal vessels, which can then lead to hemorrhage. Epistaxis is caused by platelet inactivation due to paraprotein saturation of the platelet surface.¹²³ Patients may also have paraprotein-mediated peripheral neuropathy or high-output cardiac failure due to expanded plasma volume.

Tumor morphology reveals small lymphocytes, plasmacytoid lymphocytes, and plasma cells.¹²⁴ Lymphocytes with intranuclear pseudo-inclusions of IgM called Dutcher bodies may be present. Also, plasma cells with prominent cytoplasmic globules (called Russell bodies) can be

seen. Cells are positive for pan-B-cell markers and variably positive for CD11c, CD25 and dim CD22 (81%, 71%, and 33%, respectively).¹²⁵ CD5, CD10, and CD23 are not usually expressed; however, this can be variable.¹²⁶ Neoplastic cells are positive for cytoplasmic immunoglobulin. It has been reported that t(9;14)(p13;q32) is present in 50% of cases, resulting in overexpression of the *PAX5* gene.¹²⁷ However, the frequency of this abnormality in LPL is now a matter of controversy since subsequent studies have shown it to be rarely present in LPL.^{128,129} As with other indolent lymphomas, transformation to large cell lymphoma can occur.¹³⁰

Given the rarity of LPL, there is no established standard treatment. Patients are commonly treated in a manner similar to that of other indolent B-cell NHLs. In asymptomatic patients, a watch-and-wait approach can be applied. In patients with WM, treatment should not be initiated based on the presence of a monoclonal protein alone (in the absence of hyperviscosity), but rather based on the presence of symptoms. Treatment recommendations for WM exist and may be successfully applied to patients with symptomatic LPL even if criteria for WM are not fulfilled. Alternatively, low-grade lymphoma regimens may be used to treat LPL. Effective therapies include rituximab, R-CVP, R-CHOP, as well as WM regimens such as fludarabine-, cyclophosphamide-, bortezomib-, and thalidomide-based regimens in combination with rituximab.^{131,132} For responding patients, maintenance rituximab may be of benefit.¹³³ Administration of rituximab can result in an abrupt increase in serum IgM levels causing a hyperviscosity syndrome “flare.”¹³⁴ The initial treatment for symptomatic hyperviscosity syndrome is with plasma exchange. Clinical benefit is often achieved rapidly after initiation of plasma exchange. In addition to plasma exchange, chemotherapy is typically given as well to reduce the level of malignant cells responsible for the production of the paraprotein causing the hyperviscosity syndrome.

SUMMARY

Given the long natural history of indolent B-cell NHL, a watch-and-wait approach can often be applied until patients are symptomatic from their disease. Indolent lymphomas are generally considered incurable, but with the widespread incorporation of rituximab into current regimens, the introduction of novel biological agents, and more widespread use of stem cell transplantation, long-term remissions with preserved quality of life are possible. In this era of improved treat-

ment options, some patients may achieve long-term remissions and/or survival in excess of 10 to 15 years.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.

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