Splenic Marginal Zone Lymphoma: Villous, Not Necessarily Villainous

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The article by Thieblemont and colleagues very nicely summarizes the key pathogenetic and diagnostic features and present treatment of splenic marginal zone lymphoma (SMZL). This histologic subtype of non-Hodgkin lymphoma has evolved from being an unrecognized entity in earlier classification systems (such as the Working Formulation[1]), to a provisional entity in the Revised European/American Lymphoma (REAL) classification,[2] and finally to a fully recognized distinct clinicopathologic entity in the World Health Organization (WHO) classification system.[3] The WHO classification system separates marginal zone B-cell lymphomas into three clinically distinct subtypes: nodal marginal zone lymphomas, extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas), and SMZL.

Although SMZL accounts for only approximately 2% of non-Hodgkin lymphomas,[4] it is associated with unique features that continue to build a case for an infectious/chronic inflammatory etiology in at least a percentage of patients. Although a single distinct pathway elucidating the pathogenesis of marginal zone lymphomas has not emerged, some data suggest that the cells are memory B lymphocytes, since they arise from cells in the marginal zone of secondary lymphoid follicles. In a relatively large percentage of cases, the malignant cells appear to have undergone somatic hypermutation (ie, are of post–germinal center origin), implying the presence of previous antigenic exposure. However, other data suggest the possibility that the cell of origin may be a circulating B cell that has undergone somatic hypermutation independent of the germinal center mechanism and is pre–antigen-exposed.[5] Marginal zone lymphomas are frequently associated with the presence of chronic antigenic stimulation—either infectious antigens or possibly host auto-antigens. SMZL has frequently been associated with the presence of antibodies to hepatitis C virus (HCV).[6] The presence of a transmembrane protein known as CD81 on the surface of these B cells may provide a pathway through which HCV can cause B-cell activation via the B-cell receptor.[7] Patients with SMZL may present with manifestations of autoimmune disease (eg, autoimmune hemolytic anemia/thrombocytopenia, antiphospholipid antibody syndrome) or manifestations of HCV infection (eg, cryoglobulinemia).[8,9] It appears that patients with either a monoclonal protein or immunologic manifestations of their disease may have shorter remissions than those whose disease does not have these features.[10]

As with virtually all WHO lymphoid neoplasms, the diagnosis of SMZL is based on elements of morphology (including peripheral blood villous lymphocytes when present), immunophenotype, and genetic information. The initial differential diagnosis includes essentially any entity that can produce splenomegaly, peripheral lymphocytosis, and bone marrow involvement (eg, chronic lymphocytic leukemia, hairy cell leukemia, mantle cell lymphoma, T-prolymphocytic leukemia, etc), although careful attention to the clinical picture and expert pathologic review will usually easily rule out these other entities. While no diagnostic cytogenetic abnormality is recognized, commonly observed abnormalities include 7q 31-32 allelic loss and partial trisomy 3. It has been postulated that chronic inflammation caused by ongoing antigenic stimulation could, in theory, lead to the development of reactive oxygen species, thereby damaging DNA.[11] In the specific setting of marginal zone lymphomas, it is possible that this could be the stimulus leading to the development of a number of nonspecific chromosomal abnormalities.

The diagnosis of SMZL can usually be made without splenectomy, on the basis of careful analysis of peripheral blood and bone marrow along with immunophenotyping and cytogenetics. If a diagnostic splenectomy is being contemplated, our usual practice is to vaccinate the patient against encapsulated organisms (eg, at least against Streptococcus pneumoniae with consideration of vaccination also against Haemophilus influenzae and Neisseria meningitidis) because of the spleen's
role in generating antibodies against encapsulated organisms. Staging of SMZL is based on the history and physical examination, and on examination of the bone marrow and imaging studies. Although positron emission tomography (PET) scanning may be of some use in marginal zone lymphomas, CT scanning is probably sufficient, since PET information is unlikely to alter therapeutic management. As described by Thieblemont and colleagues, the Italian Intergroup of Lymphomas study group has developed a simple prognostic scoring system that gives reasonable 5-year estimates of survival based on a low hemoglobin level, elevated lactate dehydrogenase level, and low albumin level. Other prognostic factors similar to those used in chronic lymphocytic leukemia (eg, CD38 expression, IgVH mutational status) may also be of some value, but since data about such factors are fairly limited, they are unlikely to be helpful in routine clinical practice. Also, the clinician needs to remember that the presence of poor prognostic factors does not imply the need to start therapy earlier in the absence of any routine clinical indication for treating the patient. As with any indolent lymphoma, SMZL is for all intents and purposes considered incurable with "standard" therapies. Thus, it remains completely reasonable in our opinion to watch asymptomatic or minimally symptomatic patients, reserving treatment for patients with progressive symptomatic splenomegaly or progressive cytopenias. Splenic rupture and transformation to aggressive lymphoma are recognized complications of this entity. Because the number of meaningful prospective studies is small, the literature does not provide sufficient evidence to meaningfully or critically compare various treatment options. Splenectomy is clearly associated with improvement in cytopenias. Patients with SMZL associated with hepatitis C have experienced remissions with antiviral therapy.[12] Although it would seem prudent to prescribe antiviral therapy only for symptomatic patients or patients with important or progressive liver disease, some recommend initial antiviral therapy for these patients even if they are asymptomatic/without significant liver disease. Since there is some morbidity and possible mortality (both early and late) associated with splenectomy, other therapies, such as rituximab and cytotoxic agents, have been used as single agents or in combination with good success. The article by Thieblemont et al provides a table summarizing various treatment strategies in numerous small treatment series. The use of stem-cell transplantation (SCT) would seem reasonable given that it is considered a treatment option for indolent lymphomas, but there are very few data describing outcomes for SCT in patients with SMZL.[13,14] Furthering our understanding of SMZL will clearly require enthusiastic support for multicenter prospective phase II trials, since meaningful data from randomized trials are unlikely due to the rarity of this entity.

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REFERENCES


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