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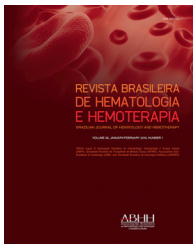

Review article

Splenic marginal zone lymphoma: a literature review of diagnostic and therapeutic challenges

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ABSTRACT

Splenic marginal zone lymphoma (SMZL) is a low-grade B-cell non-Hodgkin's lymphoma characterized by massive splenomegaly, moderate lymphocytosis with or without villous lymphocytes, rare involvement of peripheral lymph nodes and indolent clinical course. As a rare disease, with no randomized prospective trials, there is no standard of care for SMZL so far. Splenectomy has been done for many years as an attempt to control disease, but nowadays it has not been encouraged as first line because of new advances in therapy as rituximab, that are as effective with minimal toxicity. Facing these controversies, this review highlights advances in the literature regarding diagnosis, prognostic factors, treatment indications and therapeutic options.

Introduction and clinical features

Splenic marginal zone lymphoma (SMZL) is a rare indolent non-Hodgkin lymphoma (NHL) subtype that originates from B memory lymphocytes present in the marginal zone of secondary lymphoid follicles.[1–3]

Patients usually present massive splenomegaly and bone marrow involvement with minimal or absent lymphadenopathy except for the spleen hilum. There is no extranodal involvement, except for the bone marrow and liver.[3,4] About 25% of the patients are asymptomatic and the presence of B symptoms or high lactate dehydrogenase levels (LDH) at diagnosis is not usual.[5,6]

Lymphocytosis is commonly present. Cytopenias are found in 25% of the cases mostly related to hypersplenism, and less frequently to auto-antibodies or bone marrow infiltration.[3,4]

Small amounts (less than 2 g/dL) of monoclonal protein, usually immunoglobulin (Ig)M kappa, are detected in approximately one third of patients.[5,7] Hyperviscosity syndromes are not usual,[3] but 20% of patients present autoimmune hemolytic anemia and other autoimmune disorders, such as thrombocytopenia, cold agglutinin disease, circulating anticoagulants and even angioedema because of acquired C1-esterase inhibitor deficiency.[5,7,8]

The rarity of this disease and its indolent course are a challenge to determine standard care in the treatment and management of patients. There are no randomized trials, most

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of the literature are retrospective series of cases from single centers and few prospective studies have been completed or are ongoing.[8]

Epidemiology

SMZL is the second most common subtype of marginal zone lymphoma, comprising about 20% of the cases. It represents about 0.9% of all NHL and was considered a specific pathological entity only in 1991.[1,5,9]

Median age at diagnosis of SMZL is 69 years. The overall age-adjusted incidence is 0.13/100,000 habitants per year. The percentage change in age-adjusted incidence is 4.81%, with most of the patients being White.[8] Gender prevalence is controversial,[6,7] but there is an increasing trend to male predominance.[8,10,11]

The association of SMZL with hepatitis C (HCV) is common in the south of Europe,[3,12,13] and lymphoma development is usually triggered by the glycoprotein E2 of the virus that stimulates CD81 in B cells.[5,6,13] Although there are controversial data in Brazil regarding the association of HCV and lymphoma, no studies have evaluated this association.[14,15]

The International Lymphoma Epidemiology Consortium Non-Hodgkin Lymphoma Subtypes Project, with a database of 17,471 NHL cases and 23,096 controls, identified an association between SMZL and B cell activating autoimmune conditions, asthma and use of hair dye.[16]

Diagnosis

The diagnosis of SMZL can be by the analysis of pathological cells present in bone marrow with blood and spleen analysis not being essential.

Bone marrow infiltration is a very common finding (83–100%), although circulating cells are detected much less frequently (29–75%).[7] During the course of the disease, 75% of the patients will present lymphocytosis, with characteristic, but not pathognomonic, villous cells.[4,17] Bone marrow aspirate is not sufficient for diagnosis; a trephine histology with immunohistochemical analysis is required.[5]

Pathological cells of SMZL are small- to medium-sized mature B cells with round or oval nuclei and condensed chromatin, basophilic cytoplasm, and most of the cases present with typical unequal membrane projections (villi), the so-called villous cells (Figure 1).[4–7] Marrow infiltration can be nodular, interstitial or intrasinusoidal.[5]

There is no specific immunophenotypic pattern for SMZL. Pathological cells are usually positive for CD19, CD20, CD22, CD79a, CD79b, FMC7 and IgM and negative for CD5, CD10, CD43, BCL6, cyclin D1 or CD103. The expressions of CD23, IgD and cytoplasmatic Ig are variable,[6,18] usually scoring 0–2 points in the Modified Matutes scoring system.[19] CD5 are weakly positive in 10–25% of the cases, even with the co-expression of CD23 or CD43.[20] CD11c and CD25 are sometimes positive, but CD103 and CD123 are almost always negative.[4]

Bone marrow immunohistochemistry analysis reveals positivity for CD45RA, CD45RB, CD19, CD20, CD79a, PAX5/BSAP, IgD, Bcl-2, DBA-44 (CD72), TRAP and CD38.[5,21,22] IgM is usually bright, but IgD is variable.[4,6] Cells are usually negative for CD3, CD5, CD10, CD23, CD43, cyclin D1, anexin-A1 and BCL6. KI67/Mib1 has a low proliferation index with a characteristic pattern.[4,6]

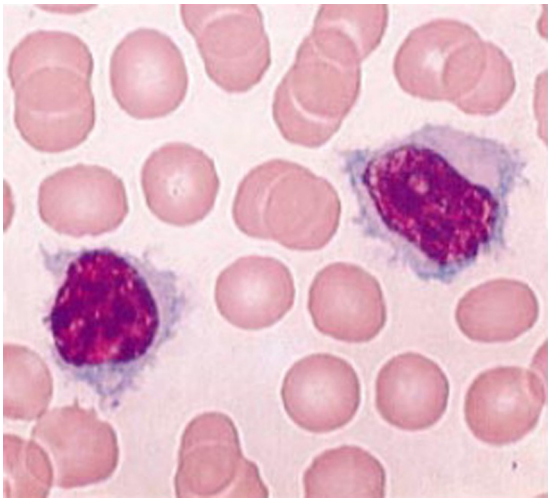

Figure 1 – Morphologic features of villous lymphocytes in patients with splenic marginal zone lymphoma.

The spleen is frequently enlarged, with a median weight of 1750 g (270–5500 g) and many grayish nodules throughout the parenchyma.[6] White pulp is expanded by neoplastic cells that surround and eventually substitute germinal centers. Nodules are composed of pathological cells, located in an inner zone of small- to medium-sized B cells with round nuclei, clumped chromatin and scanty cytoplasm. Externally there is an outer zone with medium-sized pathological cells, with more irregular nucleus outlines, dispersed chromatin and moderately clear cytoplasm. There are scattered cells in this zone resembling immunoblasts. As the disease progresses, the central germinal center becomes effaced. The red pulp is invariably enveloped to a varying degree by small aggregates of larger cells and sheets of small cells, which often occupy sinuses and cords. There can be epithelioid granulomas and plasmacytic differentiation, the former especially when there is a monoclonal serum component. Immunohistochemical findings are similar to bone marrow findings.[5,6,9]

Matutes et al. proposed minimum diagnostic criteria for SMZL:

a) When spleen pathology is available: spleen histology and immunophenotype with a modified Matutes score of <3 points.[19]
b) When the patient has clinical splenomegaly and splenectomy is not performed, it is sufficient to make the diagnosis with typical blood and bone marrow findings by morphology and immunophenotype with intrasinusoidal infiltration by $CD20^{+}$ cells.

After the diagnosis is performed, it is important to evaluate the clinical stage of the patient, with computed tomography scans and routine exams to detect comorbidities that may affect the choice of treatment. These exams should include complete blood count with differential, serologic