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Splenic marginal zone lymphoma

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A B S T R A C T

Splenic marginal zone lymphoma (SMZL) is an indolent small B-cell lymphoma involving the spleen and bone marrow characterized by a micronodular tumoral infiltration that replaces the preexisting lymphoid follicles and shows marginal zone differentiation as a distinctive finding. SMZL cases are characterized by prominent splenomegaly and bone marrow and peripheral blood infiltration. Cells in peripheral blood show a villous cytology. Bone marrow and peripheral blood characteristic features usually allow a diagnosis of SMZL to be performed. Mutational spectrum of SMZL identifies specific findings, such as 7q loss and NOTCH2 and KLF2 mutations, both genes related with marginal zone differentiation. There is a striking clinical variability in SMZL cases, dependent of the tumoral load and performance status. Specific molecular markers such as 7q loss, p53 loss/mutation, NOTCH2 and KLF2 mutations have been found to be associated with the clinical variability. Distinction from Monoclonal B-cell lymphocytosis with marginal zone phenotype is still an open issue that requires identification of precise and specific thresholds with clinical meaning.

The term splenic marginal zone lymphoma (SMZL) was initially proposed by Schmid and colleagues 1 in 1992 for a small B-cell lymphoma involving the spleen and bone marrow characterized by a micronodular tumoral infiltration that replaces the preexisting lymphoid follicles and shows marginal zone differentiation as a distinctive finding. SMZL is defined in the World Health Organization (WHO) classification as a B-cell neoplasm comprising small lymphocytes that surround and replace the splenic white pulp germinal centers, efface the follicle mantle, and merge with a peripheral (marginal) zone of larger cells, including scattered transformed blasts; both small and larger cells infiltrate the red pulp [1,2]. Most cases have a fairly typical clinical presentation characterized by prominent splenomegaly and bone marrow and peripheral blood infiltration. Cells in peripheral blood can frequently be recognized by the villous cytology; this and other findings confirming that SMZL and splenic lymphoma with villous lymphocytes basically represent the same entity [3–6].

Despite the name suggesting a common link with other marginal zone-derived lymphoproliferative neoplasms, the clinical, immunophenotypic, and genetic features of SMZL are different from other MZLs, indicating that SMZL is a distinct clinicopathologic entity, basically unrelated to MALT or nodal MZL. The incidence of SMZL may be underestimated because splenectomy is not commonly performed in many cases of low-grade lymphoma, and establishing a precise diagnosis in bone marrow or peripheral blood still has some limitations, making it difficult to compare the incidence of this disorder with that of other B-cell lymphomas. Nevertheless taking all the above into consideration, SMZL appears to account for about 1%–2.7% of all lymphomas [2,5,7,8].

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Interestingly, a small fraction of SMZL patients harbor hepatitis C virus, and therapy directed against hepatitis C seems to influence control of the tumor load in these patients, suggesting that infectious agents play a role in the pathogenesis of SMZL [9]. The frequency of HCV infection associated with SMZL is definitely higher in South Italy, where it has been found in up to 3.1% of cases [10]. This role of infectious agents is also supported by the similarities evident in SMZL and so-called hyper-reactive malarial splenomegaly [11].

Clinical features

The median age at diagnosis is around 65 years, ranging from 30 to 90 years, with a slight female predominance reported in some series [8,12]. Most of the patients are asymptomatic and more frequently the disease runs an indolent course. Splenomegaly is the most common clinical sign, observed in 75% of patients; while anemia, thrombocytopenia, or leukocytosis has been reported in 25% of cases. Hemolytic anemia and other autoimmune disorders are found in 10%–15% of patients [7,13,14]. SMZL is infrequently diagnosed incidentally on routine examination, and some of the cases thus described could represent monoclonal B-lymphocytosis with marginal zone phenotype, a condition that could precede some of these SMZL cases [15].

Almost without exception, SMZL involves the bone marrow at diagnosis, and about a third of patients have liver involvement. Tumor involvement of peripheral blood (defined as the presence of absolute lymphocytosis or >5% neoplastic lymphocytes in peripheral blood) was detected in 68% of cases by Chacon's group [13] and in 57% by Berger' and co-workers [14]. Abdominal lymphadenopathy was observed in 25%; peripheral lymphadenopathy was observed more rarely (17%). Because of the high frequency of bone marrow or liver involvement, most patients are at Ann Arbor stage IV at diagnosis. Serum paraproteinemia (usually IgM) is evident in 10%–28% of cases [7,13,14].

Survival rate in SMZL is strongly dependent on the clinical stage at diagnosis and the treatment received, varying from 42 to 95% 10-years survival probability [10,16,17].

Morphology

When the spleen is removed for the diagnosis or treatment of SMZL, splenic histology is characterized by a micronodular lymphoid infiltrate in which white pulp follicles are increased in both size and number, frequently associated with a variable degree of red pulp involvement (Fig. 1). The follicles typically have a biphasic appearance, with the presence of both a small

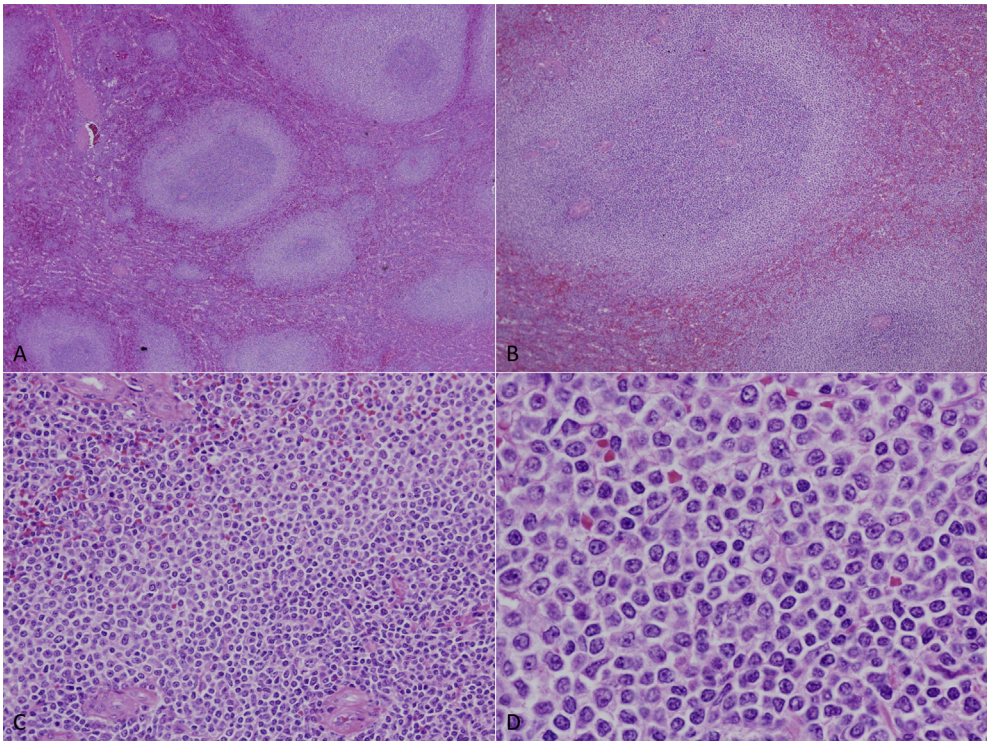

Fig. 1. Splenic marginal zone lymphoma morphology in the spleen. A, Low magnification shows marginal zone differentiation and biphasic cytology, with pale-staining cells in the marginal zone, darker cells in the interior of the follicle, and occasional pale central areas, indicating replaced germinal centers. B,C, Replacement of lymphoid follicles by neoplastic cells. D, High magnification of the biphasic cytology, characteristic of splenic infiltration by SMZL.

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