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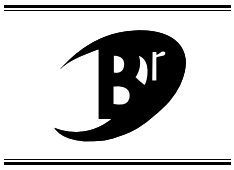

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REVIEW

Splenic marginal zone lymphoma

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Treatment

Summary Splenic marginal zone lymphoma (SMZL) is an indolent B cell malignancy usually involving spleen, bone marrow and blood. The disease presents as an incidental finding or with symptoms of splenic enlargement or anaemia. Diagnosis is based on a combination of lymphocyte morphology, immunophenotype and marrow and /or splenic histology. There is no genetic abnormality specific for SMZL, but deletions of chromosome 7q are the commonest abnormality and are found in 30-50% of cases. SMZL cells may have either mutated or unmutated immunoglobulin variable region genes and probably arise from different subsets of splenic marginal zone B cells. Prognostic factors are poorly defined and only loss or mutation of the *p53* gene is consistently associated with a poor outcome. Therapeutic options include splenectomy, splenic irradiation, alkylating agents, purine analogues or anti CD20 antibody. The median survival is 10–13 years and most disease-related deaths are associated with transformation to diffuse large cell lymphoma.

Introduction

The existence of an indolent B cell disorder characterised by splenomegaly and circulating lymphocytes with an irregular cytoplasmic border, distinct from hairy cell leukaemia, was first reported in 1979.[1] In 1987 Melo et al.[2] introduced the term splenic lymphoma with villous lymphocytes (SLVL) to describe this condition, which was incorporated as a distinct entity in the French-American-British proposal for the classification of chronic B cell leukaemias in 1989.[3] Schmid et al.[4] first used the term splenic marginal zone lymphoma (SMZL) to describe the splenic histology in four patients who presented with splenomegaly and a lymphoid infiltrate in the marrow. In 1994[5] the same group confirmed that the splenic histology of patients diagnosed as SLVL who subsequently underwent splenectomy was typical of SMZL. SMZL was included as a provisional entity in the Revised European-American Classification of Lymphoid Neoplasms in 1994,[6] and as a separate entity, distinct from marginal zone lymphomas originating in mucosa associated lymphoid tissue or lymph nodes, in the World Health Organisation classification published in 2001.[7]

It is now possible to predict that patients presenting with SLVL and splenomegaly have SMZL

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without the need for splenectomy, based on careful morphological and immunophenotypic examination of the blood and bone marrow, supplemented in difficult cases by cytogenetic and/or molecular genetic studies. This is analogous to the relationship between chronic lymphocytic leukaemia and small lymphocytic lymphoma. In this review we will use the term SMZL to encompass both SMZL and SLVL unless referring to articles which use the term SLVL. However it is important to note that not all cases of SLVL present with or develop palpable splenomegaly and the circulating neoplastic lymphocytes in SMZL do not always have cytoplasmic villi.

Clinical features

SMZL is a disease of the elderly; the median age at presentation is approximately 65 years while virtually all patients are aged greater than 50 years. The reported incidence is 1–2% of non-Hodgkin lymphomas,[8,9] but these figures do not include the more benign cases which do not undergo splenectomy or require any form of treatment. It is a disorder, which characteristically involves the spleen, bone marrow and peripheral blood. A typical patient will present with symptoms of fatigue and/or abdominal discomfort, and have prominent splenomegaly, a moderate degree of bone marrow infiltration and circulating cells evident on their peripheral blood smears.[9,10] Palpable lymphadenopathy is uncommon but involvement of the splenic hilar lymph nodes is seen in the majority of cases. Anaemia and thrombocytopenia are common at presentation but are frequently the result of hypersplenism rather than bone marrow infiltration. A paraprotein, which rarely exceeds 30gm/l, is detectable in the serum of up to a third of patients; most commonly this is of IgM type but IgG and very rarely IgA paraproteins are also seen (Table 1).[1,9,11–13]

Autoimmune phenomena are found in 10% of patients and may be the presenting feature. These include warm-type autoimmune haemolysis, cold agglutinins, immune thrombocytopenia, anti cardiolipin antibodies, lupus anticoagulant and acquired von Willebrand's disease.[11,12,14–17] Rarely patients may develop the symptoms of angio-oedema due to acquired C1 esterase inhibitor deficiency.[18]

Approximately 10% of cases undergo transformation to a high-grade lymphoma, with median times from diagnosis to transformation of two to four years. Features, which suggest disease transformation, include the onset of B symptoms,

Table 1 Clinical features of SMZL/SLVL.

	Mulligan[65]	Troussard[1]	Parry-Jones[12]	Chacon[11]	Berger[13]					Thieblemont[19]			Iannito[57]
	SLVL	SLVL	SLVL	SMZL	SLVL Spleen	MZL* Leukaemia	Nodal	Disseminated		MZL* Non-SLVL	SLVL		
No. of patients	50	100	129	60	59	8	37	20		71	10		57
M/F ratio	1.77	0.67	0.9	1.72	0.78	0.6	0/76	1.5					1.59
Median age	68.4	70	69	63						63	75		61.5
Splenomegaly	100%	?100%	77%	73%	100%	0%	0%	95%					89%
Blood involved $>4.0 \times 10^9$/l	100%	91%	75%	68%	57%	75%	11%	45%		37%	70%		37%
Serum IgM component	Not stated	28%	22%		24%	0%	8%	12%		45%	18%		27%

* Non-splenic marginal zone lymphomas.