short report
Haematologica 1996; 81:44-46

SPLENIC MARGINAL ZONE CELL LYMPHOMA INVOLVING LIVER AND BONE MARROW. REPORT OF A CASE WITH PROTRACTED FOLLOW-UP, SHOWING PROGRESSIVE DISAPPEARANCE OF THE LYMPHOMA AFTER SPLENECTOMY

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ABSTRACT

We report the case of a 42-year-old man who presented with B-symptoms, moderate splenomegaly and multiple nodules in the liver. Histologically, lymphocytic infiltrates were seen in the portal spaces and sinusoids of the liver and in the paratrabecular areas of the bone marrow. After excision, the spleen showed minimal disturbance of architecture with an expansion of the follicular marginal zones. These findings were considered inconclusive for lymphoma and the patient was treated only with non-steroidal anti-inflammatory drugs for persisting fever. Five months after splenectomy, a bone marrow biopsy still showed diffuse lymphoid infiltrates. From then on, the patient's condition improved with no further evidence of disease. Ten years after splenectomy the case was reconsidered as a splenic marginal cell lymphoma, indolent variant. Immunohistochemical and gene rearrangement studies demonstrated the monoclonality of the splenic proliferation, supporting the diagnosis. A further bone marrow biopsy did not detect residual lymphoid infiltrates. This case confirms that splenic marginal zone cell lymphoma may have a deceptively favorable course, even when presenting at an advanced stage. Moreover, it indicates that extrasplenic localizations of the lymphoma may persist for a long while after splenectomy but may vanish over time without therapy.

Key words: spleen, splenic marginal zone lymphoma, low-grade lymphoma

Splenic marginal zone cell lymphoma (SMRZCL) is a recently described malignant lymphoma arising from a lymphoid compartment unique to the spleen.[1,2] Most SMRZCLs have been reported to cause massive splenomegaly, to involve bone marrow, and to spread occasionally to distant lymph nodes.[1-3] Some SMRZCL cases have been assigned to an indolent variant with minimal histological and clinical aggressiveness.[4]

Here we report an indolent SMRZCL which presented with B-symptoms and extrasplenic diffusion, persisted in the bone marrow after splenectomy, and eventually vanished without any chemotherapy.

Case report

In October 1986 a 42-year-old male was admitted to the hospital, complaining of persistent fever, asthenia and weight loss. No relevant findings were noted at physical examination. Laboratory analyses demonstrated elevated ESR (111 mm/h) and moderately increased alkaline phosphatase and γ-glutamyl transferase (respectively, 487 U/L and 79 U/L). Lactate dehydrogenase, serum copper, serum electrophoresis and immunoelectrophoresis were within normal limits. Blood cell count showed RBC 5.42×10^{12}/L and WBC 10.9×10^{9}/L with N 64%, E 1%, L 29% and M 6%). Computerized tomography of the abdomen disclosed moder-

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Received October 6, 1995; accepted November 29, 1995.

ate enlargement of the liver, spleen and one para-aortic lymph node. At laparoscopy, multiple small whitish nodules were detected on the hepatic surface, which at histologic examination were found to be composed of nodular lymphocytic aggregates in portal spaces with sinusoid infiltration. A minute epithelioid cell granuloma was also seen. A bone marrow biopsy showed nodular interstitial and paratrabecular infiltrates of medium-sized lymphoid cells with slightly indented nuclei, clearly distinguishable for the abundance of cytoplasm (Figure 1). Since lymphoma was suspected a splenectomy was then performed. The excised spleen weighed 300 g and showed uniform expansion without architectural distortion of follicular marginal zones (MRZ) or periarteriolar lymphoid sheaths (Figure 2). Follicles were found to be moderately enlarged and were either completely substituted by MRZ cell proliferation or showed hyalinized remnants of germinal centers with some residual mantle zone cells. Red pulp appeared unaffected and sharply demarcated with respect to the white pulp proliferation.

Cytologically, MRZ cells were medium-sized and monomorphous, with round to oval, bland-appearing nuclei and ample, pale eosinophilic cytoplasm. These findings were considered inconclusive for a diagnosis of lymphoma, and the patient was discharged from the hospital with anti-inflammatory non-steroid drugs being the only therapy prescribed. In March 1987, he was admitted again for persistence of fever. Laboratory tests showed ESR, alkaline phosphatase and γ-glutamyl transferase above normal limits. A further bone marrow biopsy disclosed persistent nodular and diffuse lymphocytic infiltrates substituting up to 50 per cent of the normal population. From then on, the patient's condition improved and he has remained in good health through May 1995, when his case was reconsidered.

Histological slides were reviewed and a diagnosis of SMRZCL of the indolent variant was formulated, according to a recent report.[4] This diagnosis was confirmed by paraffin section immunohistochemistry with a microwave antigen retrieval method,[5] which showed monotypic IgM/λ on the surface of lymphoid cells in both spleen and liver specimens. Immunohistochemical and molecular analyses could not be performed on bone marrow sections since biopsies were glycol methacrylate embedded. However, the extent of bone marrow substitution and the striking cytologic similarities between the lymphoid cells in the bone marrow infiltrates and in the spleen (i.e. medium-sized lymphocytes with ample, pale cytoplasm and slightly indented, round to oval nuclei) were considered reliable criteria for SMRZCL involvement.

In a subsequent study performed in collaboration with the Institute of Pathology of the University of Würzburg, this and other SMRZ-

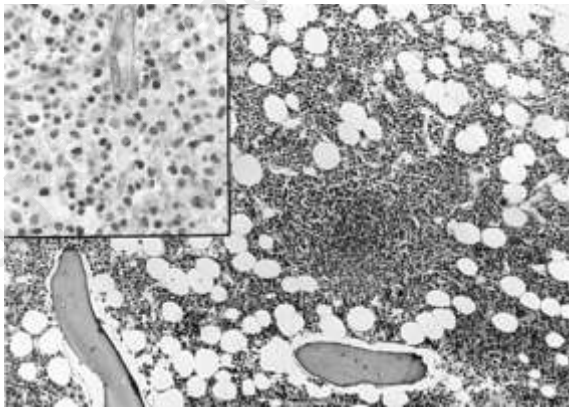

Figure 1. Nodular lymphoid infiltrate in the bone marrow (Dominici stain; original magnification: x 20). Inset: the infiltrate is composed of medium-sized lymphoid cells with round to oval nuclei, clearly distinguishable for the abundance of cytoplasm (Dominici stain; original magnification: x128).

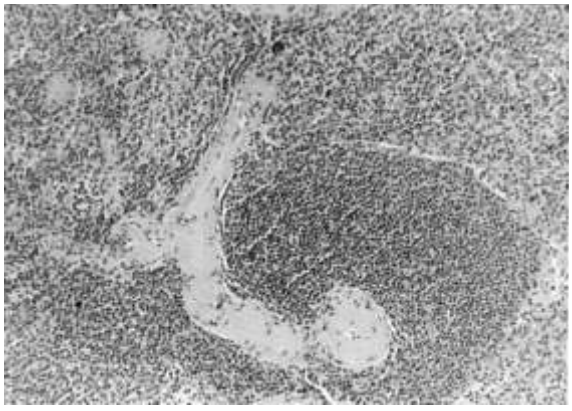

Figure 2. Splenic marginal zone cell lymphoma appears to be strictly confined to the white pulp-substituting follicles and periarteriolar lymphoid sheaths (Hematoxylin and eosin; original magnification: x32).

CL cases were submitted to molecular investigation. DNA extracted from spleen paraffin sections and amplified by polymerase chain reaction (PCR) with specific consensus primers for the variable and joining regions of the immunoglobulin heavy chain gene gave positive results for clonal rearrangement in all lymphomas.[6] Ultimately, extensive work-up studies did not detect residual involvement of the bone marrow or clinical or laboratory anomalies.

Discussion

Although it has only been reported in a small number of cases, SMRZCL was considered important enough to be included in two recent classifications of lymphoid neoplasms.[7,8] It was initially described as an aggressive lymphoma with poor prognosis[1] but was later found to behave frequently in an indolent manner.[3,4] Our case has the longest follow-up of those reported in the literature and confirms that SMRZCL may be characterized by a deceptively favorable course.[3,4] This report indicates that indolent SMRZCL is not exclusively a lymphoma of elderly patients, as suggested from previous reports.[3,4] Moreover, it shows that indolent SMRZCL may present with B-symptoms as aggressive cases do.[1] Our case showed lactate dehydrogenase values within normal limits, a finding coherent with a low degree of malignancy rarely observed in advanced lymphomas.[9] Bone marrow involvement has been reported in most SMRZCL cases,[2,3] but was not previously described in indolent variant SMRZCLs.[4]

Our case confirms that in SMRZCL bone marrow involvement is not related to a more severe prognosis[3] and does not represent a feature that discriminates aggressive from indolent lymphomas. The presence of bone marrow infiltrates in a biopsy taken five months after splenectomy indicates that SMRZCL may persist after removal of the main neoplastic pool. Moreover, the subsequent disappearance of bone marrow involvement suggests that SMRZCL may regress without any therapy and recalls what is observed in *vanishing* gastric lymphomas.[10] From a pathological point of view, our case confirms that some SMRZCLs may induce such subtle changes in splenic morphology as to be confused with reactive MRZ expansions.[3] These findings indicate that SMRZCL can easily be underdiagnosed and therefore may be more frequent than expected from the literature. The evidence of hepatic involvement, also reported in two other cases,[2,4] indicates that the liver may be a rather common site of secondary SMRZCL localization. Interestingly enough, we found a histological pattern of liver involvement reminiscent of hairy cell leukemia,[11] another lymphoma of proposed MRZ derivation.[12]

Finally, the presence of an epithelioid microgranuloma in the liver biopsy confirms that this histiocytic reaction is a frequent finding of potential diagnostic importance, in light of what is observed in spleens and extrasplenic tissues involved by SMRZCL.[3]

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