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A Single-center Experience in Splenic Diffuse Red Pulp Lymphoma Diagnosis

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Abstract

The World Health Organization 2008 classification highlighted a new nosology—splenic diffuse red pulp lymphoma (SDRPL) with clinical and laboratory features similar to both splenic marginal zone lymphoma and hairy cell leukemia (HCL) and variant form of HCL. Experience of hematologists on the diagnosis and differential diagnosis of SDRPL is extremely limited. The aim of our report was to characterize the clinical and immunomorphologic features of SDRPL on our own observations. During 2013-2014, in National Research Center for Hematology, 87 spleen specimens removed from various B-cell lymphomas were analyzed. In four (4.6%) cases, the diagnosis SDRPL was made based on morphologic, immunohistochemical, immunophenotypic, molecular examination of spleen biopsies, blood and bone marrow samples. In all cases of SDRPL were observed significant splenomegaly, lymphocytosis from 56% to 94% (in two cases with leukocytosis 55.000 and 75.000 109/l). The circulating "villous" lymphocytes phenotype was CD20+ (bright), CD11c+/±, CD103 (weakly)+/±, LAIR-1+, CD25−, CD5−, CD10−, and CD23−. Mutation BRAFV600E was not detected. Bone marrow with minor lymphoid CD20+, CD25−, Annexin1−, Cyclin D1− cell infiltration. The average weight of the spleen was 3900 g (1450-9500 g), and morphologically, there was revealed lymphoid infiltration of red pulp with phenotype CD20+, DBA.44+, CD25−, Annexin1−, Cyclin D1−, CD103−, CD123−, CD27−, focal SD11c± and TRAP±. Now patients are observed in remission: two patients after splenectomy, two after splenectomy and cladribine+rituximab chemotherapy. SRDPL—a rare lymphoma that is suspected in the cases with significant splenomegaly and lymphocytosis with villous lymphocytes forms that have only a part of the classic markers HCL, with minor bone marrow infiltration. The standard diagnosis and treatment is splenectomy. Differential diagnosis of SMZL and HCL has clear criteria, but criteria of differentiation with variant HCL are still unknown.

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Introduction

The spleen can be involved in the pathologic process of a variety of lymphoproliferative diseases, both aggressive and indolent. Indolent lymphoproliferative disease with predominant involvement of the spleen was until recently attributed to 2 entities: splenic marginal zone lymphoma (SMZL) and hairy cell leukemia (HCL), including a variant form of HCL (vHCL). These diseases have a similar clinical presentation in many respects but have a different immunophenotype in the lymphoid cells, and the pattern of the splenic involvement also differs—to defeat the white pulp in SMZL and the red pulp in HCL and vHCL.[1-6] However, cases of disease with clinical and laboratory features similar to both SMZL and HCL have been regularly detected.[7-9] The 2008 World Health Organization classification for B-cell indolent lymphomas of the spleen that do not meet the description of the existing entities introduced a preliminary category termed "unclassified splenic lymphoma/leukemia." The category of unclassified splenic lymphoma/leukemia currently includes 2 diseases: splenic diffuse red pulp lymphoma (SDRPL) and vHCL.[10] At present, only a few cases of SDRPL have been reported. Also, in this pathologic entity has been characterized as rare (< 1% of all lymphomas) and having an indolent course.[7,11-13]

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The typical signs of SDRPL include massive splenomegaly, leukocytosis with lymphocytosis, a predominantly older patient age, with some male predominance. However, the clinical signs are not different from those of indolent lymphoproliferative diseases with splenic involvement. Therefore, morphologic, phenotypic, and molecular methods play a substantial role in the diagnosis of these diseases.[1,7,14] However, the interpretation of the results has been associated with considerable difficulties owing to the frequent detection of common markers among these diseases.

Materials and Methods

During 2013 to 2014, at the National Research Center for Hematology, 87 splenectomies were performed in patients with various B-cell lymphomas were analyzed. Of the 87 patients, 4 had findings significant for SDRPL (2 men and 2 women). Their median age was 58.5 years (range, 52-71 years). Diagnostic bone marrow and/or peripheral blood samples were taken from all patients. The diagnosis was determined from the results of morphologic examinations of the peripheral blood and bone marrow smears and immunophenotyping by flow cytometry using an antibody panel against the following antigens: CD3, $CD16^{+}CD56$, CD14, CD45, CD20, CD23, CD19, CD5, CD43, CD10, CD38, CD19, sIgκ, sIgλ, CD19, CD103, CD11c, CD25, CD19, FMC-7, CD23, and leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1). The immunophenotype was determined using standard methods of flow cytometry to FACSCanto II (Becton Dickinson, Franklin Lakes, NJ) using the FACSDiva software. Immunohistochemical studies were performed on formalin-fixed tissues in paraffin blocks by standard methods using a panel of the following antibodies: CD20, CD3, CD25, CD11c, CD103, CD27, CD123, DBA.44, annexin 1, and cyclin D1. To exclude similar lymphoproliferative disorders, the tartrate-resistant acid phosphatase (TRAP) level, mutation of V600E in the *BRAF* gene in lymphoid cells by allele-specific polymerase chain reaction in real time, and identification of the M-component by electrophoresis of serum proteins were performed.

Results

Patient Characteristics

The important patient characteristics are summarized in Table 1. The diagnosis of SDRPL was determined by examination of the splenic specimens in 4 patients, 2 men and 2 women, with a median age of 58.5 years. All 4 patients had clinical signs of disease that were absent or scarce (a minor weakness); thus, the disease was found accidentally from blood test results and/or abdominal ultrasound findings. All patients had severe, but asymptomatic, splenomegaly (in 1 patient, enlargement of the spleen reached to the right iliac crest), without an increase of the visceral or peripheral lymph nodes.

The blood test results for all patients revealed lymphocytosis with a normal or high count of leukocytes. The lymphocyte count ranged from 56% to 94%, and the villous lymphocyte count ranged from 12% to 85%. Monocytopenia was observed in only 1 patient. The hemoglobin level was normal or slightly reduced to 119 g/L. Thrombocytopenia was found in all 4 patients. Involvement of the bone marrow was minimal and was seen morphologically only in 2 patients but was present immunohistochemically in all 4 patients.

Table 1 Patient Characteristics and Laboratory Features

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Female	Male	Male
Age (years)	71	58	53	52
B-cell symptoms	Absent	Absent	Absent	Absent
Splenomegaly (weight, g)	1450	2450	9500	2200
Positive lymph nodes	Absent	Absent	Absent	Absent
Hemoglobin (g/L)	119	119	124	137
Leukocytes ($\times 10^9$/L)	5.0	5.0	55.0	75.0
Platelets ($\times 10^9$/L)	80.0	126.0	42.0	130.0
Lymphocytes (%)	81	56	94	77
Monocytes (%)	3.0	7.0	0	14.0
Bone marrow histologic finding (lymphoid infiltration)	Detected only by IHC	Focal-interstitial	Mild interstitial	Detected only by IHC
TRAP	Slight presence	Absent	Absent	Absent
BRAF V600E mutation	Absent	Absent	Absent	Absent
M-component	Absent	Absent	Absent	Absent

Abbreviations: IHC = immunohistochemistry; TRAP = tartrate-resistant acid phosphatase.

TRAP in the blood lymphoid cells was absent in 3 patients and was identified in a small percentage of cells in 1 patient. A V600E mutation of the *BRAF* gene and M-component were not revealed in any of the 4 patients.

Morphology and Immunophenotype

Atypical lymphoid cells, medium size with rounded hyperchromatic nucleus and wide cytoplasm with villi, were detected in all 4 patients (Figure 1A). Histologic examination of the spleen showed a violation of its structure, a reduction of follicles, and sharp plethora of red pulp. The strands of red pulp revealed diffuse infiltration of small- and medium-size lymphoid cells with rounded-oval and irregularly shaped nuclei, and moderate light cytoplasm (Figure 1B).

The histologic examination of the bone marrow in 2 cases (patients 1 and 4) revealed the absence of lymphoid infiltration by morphologic examination but was identified by immunohistochemical study. In the other 2 patients, moderate or focal interstitial lymphoid infiltration of small-size cells with round-oval and slightly irregularly shaped nuclei and moderate light cytoplasm were found (Figure 1C). Foci of fibrosis were found in only 1 patient (patient 3).

Immunohistochemical study of the bone marrow and spleen revealed monomorphic expression of CD20 and expression of DBA.44, without expression of CD25, annexin 1, cyclin D1, CD103, CD123, or CD27. Moderate or weak expression of the markers CD11c and TRAP was detected in a few lymphoid cells.

The immunophenotype of the blood cells, bone marrow, and spleen were the same in all 4 patients. To identify monoclonality, the immunoglobulin light chains were studied. In 2 cases, a κ clone and 2 λ clones of B lymphocytes were present, expressing CD20 (bright), CD11c, and LAIR-1, with moderate or weak expression of CD103, without expression of CD25, CD5, CD10, or CD23.