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Case Report

Splenic diffuse red pulp small B-cell lymphoma in an Asian female patient with review of literature

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Abstract: Splenic diffuse red pulp small B-cell lymphoma, as a provisional entity, is an uncommon lymphoma with only two series and five individual cases reported. The peripheral blood, bone marrow and spleen are involved in almost cases at diagnosis. It is usually diagnosed by spleen histopathologic examinations. We report one case of an Asian female patient who presented with both typical and specific clinical features, which helps us further understand the disease.

Keywords: Splenic diffuse red pulp small B-cell lymphoma, literature review

Introduction

Splenic diffuse red pulp small B-cell lymphoma (SDRPL) is recognized as a provisional entity of the unclassifiable splenic lymphoma category in the recent 2008 WHO classification [1]. SDRPL is an uncommon B-cell lymphoma as only two series and five individual cases have been described [2-5]. Cases are typically diagnosed at clinical stage IV, usually involve the peripheral blood, bone marrow and spleen, and scarcely manifest as pancytopenia. Presently, the diagnostic criteria for SDRPL are mainly based on spleen histopathologic examinations, which show diffuse infiltration of the splenic red pulp by monomorphous cells with a characteristic immunophenotype [4]. The diagnostic and therapeutic recommendations for SDRPL have not been established due to a lack of clinical data and systematic studies [6]. We retrospectively studied one case of an Asian female patient who presented with fatigue and entered remission after splenectomy but relapsed two years later and was diagnosed with SDRPL by spleen histopathologic examination, which has never been reported before. This case study is useful for gaining a better understanding of the disease and for providing insight into the pathogenic mechanisms of SDRPL to develop new therapeutic options.

Case report

A 50-year-old Asian female patient originally presented with fatigue in 2011 and went to the hospital due to feelings of weakness one year later. A complete blood count (CBC) revealed marked pancytopenia, with a leukocyte count of 1.2*10^9/L, a platelet count of 32*10^9/L and a hemoglobin value of 87 g/L (leukocytopenia: WBC <4*10^9/L, thrombocytopenia: PLT <100*10^9/L, and anemia: Hb <100 g/L). A CT scan showed splenomegaly, and serology for HBV infection was positive. The patient underwent a splenectomy on Aug 8th, 2012, and the postoperative pathologic diagnosis was unknown. The patient improved after surgery, with a CBC on Sep 6th, 2012 that showed the following: WBC 4.6*10^9/L, PLT 277*10^9/L and Hb 108 g/L. However, she again reported a chief complaint of fatigue, as well as vertigo, with no nausea or vomiting, fever or palpitations, on Nov 24th, 2014. A CBC revealed pancytopenia, as well as the following: WBC of 3.8*10^9/L, PLT of 59*10^9/L, and Hb of 45 g/L, as well as highly increased proportion of lymphocytes. CT

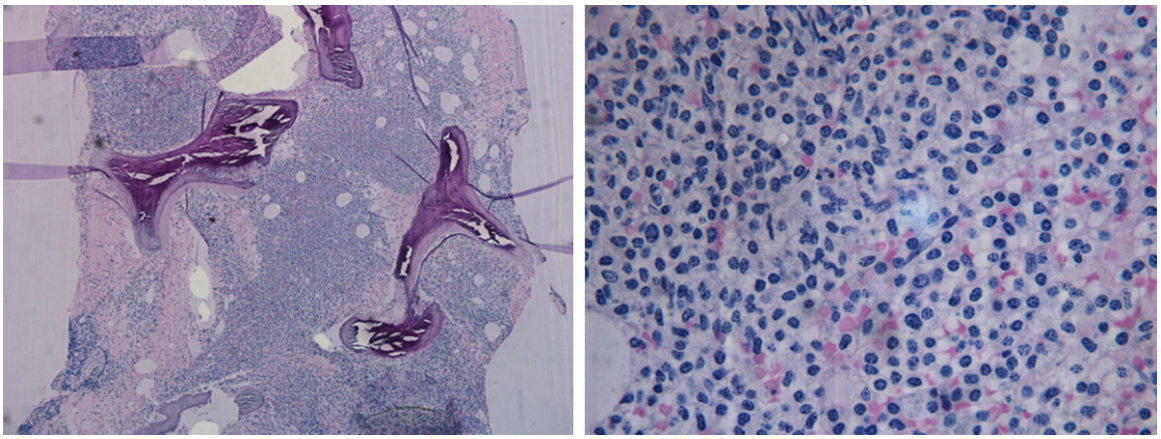

Figure 1. Bone marrow biopsy: interstitial infiltration by small round plasmacytoid cells with clumped chromatin and basophilic cytoplasm (hematoxylin-eosin, original magnification: the left ×10, the right ×100).

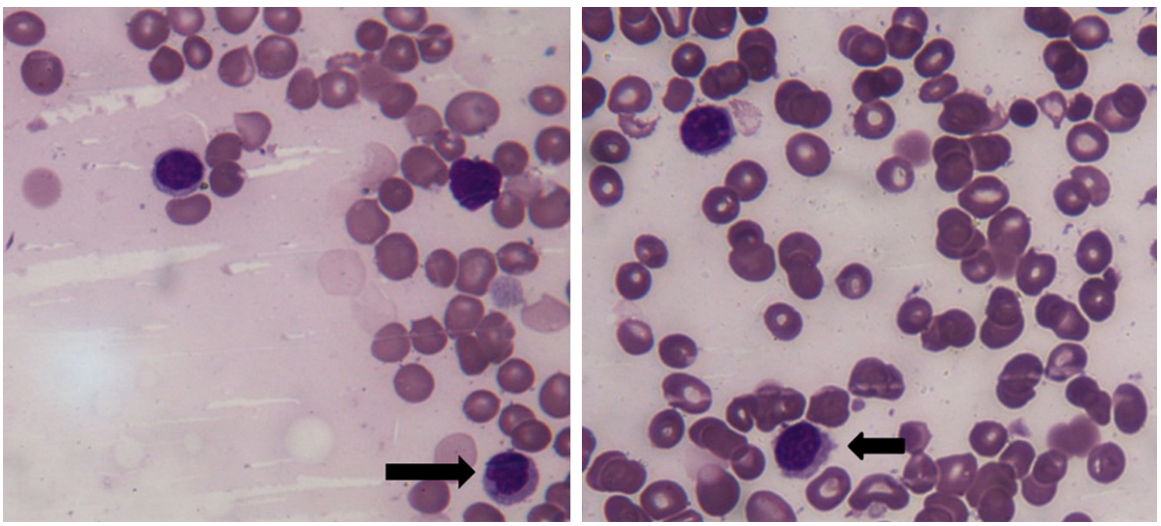

Figure 2. Cytologic analysis of bone marrow: large-sized cells with notched nuclei and clumped chromatin (long arrow) and cells with broad-based cytoplasmic projections (short arrow) (hematoxylin-eosin, original magnification: ×100).

scans demonstrated axillary, mediastinal, abdominal and groin lymphadenopathy, which has been rarely reported.

A bone marrow biopsy (BMB) revealed a pattern of interstitial tumoral infiltration of proliferating small round cells with round hyperchromatic nuclei, clumped chromatin and basophilic cytoplasm, with a plasmacytoid appearance (**Figure 1**). Only a few cells had prominent nucleoli, and no abnormalities were apparent in the megakaryocytes. Moreover, staining for reticulin fibers demonstrated partial mild fibrosis. Two repeated cytologic examinations of the bone marrow showed active hyperplasia. In particular, the lymphocyte proportion increased significantly, ranging from 85.5% to 89.5%. A slice of cells had broad-based cytoplasmic projections, and only approximately 1-2% of lymphocytes were large-sized, with notched nuclei and clumped chromatin (**Figure 2**). Bone marrow flow cytometry gated on cells expressing CD45, which is a common leukocyte antigen, showed that the majority of cells (76%) were abnormal lymphocytes. CD19, CD20, and CD22 were highly expressed in the lymphocyte population, whereas CD11c, CD25, CD23, CD103, CD123, FMC7, CD56, CD10, CD16, and CD33 were almost completely negative. In addition, an analysis of immunoglobulin light-chain expres-

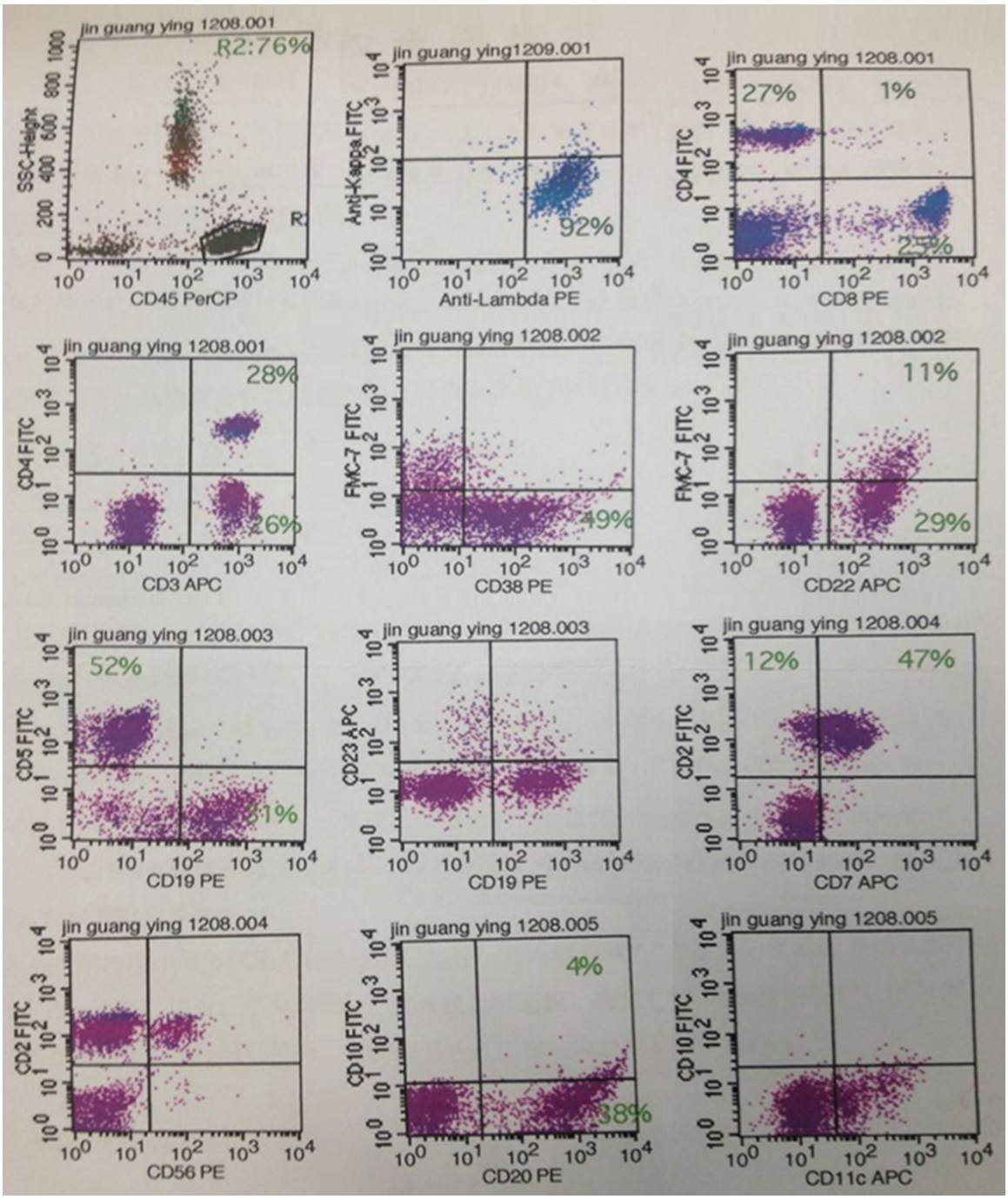

Figure 3. Flow cytometry of bone marrow: high expression of CD19, CD20, CD22 and lambda.

sion demonstrated that lambda was weakly positive, whereas kappa was negative. Ninety-two percent of the CD19+ cells were lambda+ and completely kappa- (**Figure 3**). Bone marrow immunohistochemistry showed a diffuse pattern with CD20+ and CD79a+ cells. Cells faintly expressed CD23, cyclin D1, CD3 and CD5. The expression of CD10 and TdT was negative.

The histopathology of the formalin-fixed spleen resected two years ago demonstrated mildly atrophic white pulp and dilated red pulp with sinusoidal congestion by diffuse infiltration of monomorphic small lymphocytes, which had slightly irregular nuclei. No morphologic evidence of SMZL or HCL was present. Spleen section immunohistochemistry showed that

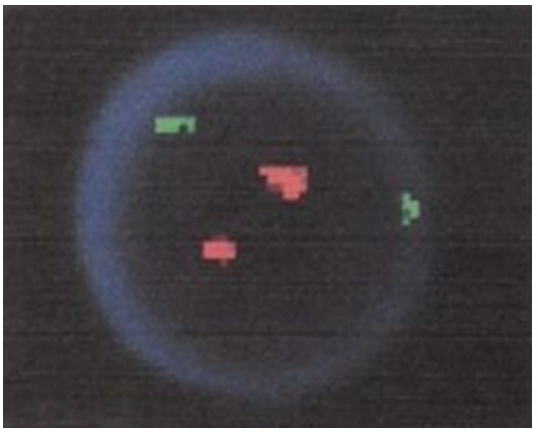

Figure 4. Fluorescence in situ hybridization of bone marrow: no signal of the IGH/CCND1 fusion gene was observed.

the lymphoid cells had a CD20+, CD79a+, CD3-, CD7-, MPO-, CD68-, CD61-, F8-, TdT-, CD117- and CD34- phenotype. Giemsa-staining was indeterminate.

Immunoglobulin heavy chain (IgH) and T cell receptor (TCR) rearrangements were absent in the spleen specimens. However, the amplified clonal IgH rearrangements in bone marrow were IGH-FR2, IGH-DH, IGκ-VJ and IGκ-V/in. A fluorescence in situ hybridization (FISH) assay for the presence of the IGH/CCND1 fusion gene caused by a t(11;14) was negative (**Figure 4**).

Another CBC after admission to our hospital demonstrated an improved blood count. Considering that the patient exhibited no obvious discomfort and the more benign prognosis of SDRPL, the patient received a small dose of IFNα and was asked to attend monthly follow-up visits after discharge from hospital. Thus far, the patient has survived without further disease progression.

Discussion

SDRPL is a rare disorder that accounts for less than 1% of non-Hodgkin lymphoma, 9-10% of spleen B-cell lymphoma, and approximately 0.5% of all chronic lymphoid malignancies. Male patients predominate, with a male/female ratio of 1.64 to 2.4. The median age is 65.5 to 77 years [3, 4]. Patients suffering from SDRPL have no peculiar clinical presentation and usually present with splenomegaly, moderate lymphocytosis, infrequent B symptoms and rare pancytopenia. The peripheral blood, bone marrow and spleen are involved in almost cases at diagnosis. Hilar splenic lymph nodes are frequently reported, whereas peripheral lymph nodes are absent [4]. The majority of blood-circulating neoplastic cells are small to medium-sized, with round nuclei, clumped chromatin and broad-based villous cytoplasm [3, 4]. Bone marrow biopsy histopathology exhibits a pure or an intra-sinusoidal/interstitial mixed pattern of neoplastic lymphocytic infiltration by small cells with round to oval nuclei and clumped chromatin [6]. Spleen histology and cytology show a purely diffuse pattern of splenic red pulp by monomorphous small cells with small round nuclei, small or invisible nucleoli and pale cytoplasm [2, 4]. Lymphoma cells usually have a CD19+, CD20+, CD22+, CD23-, bcl6-, Annexin1-, CD5-, CD103-, CD123-, CD23-, and CD10- phenotype and frequently express DBA 44, IgG, FMC7 and CD11c. IgH rearrangement shows a biased usage of the V3-4 segment [3, 4]. Spleen histopathologic examination remains the gold standard for the diagnosis of SDRPL due to the peculiar features noted in spleen specimens. No therapeutic recommendations formally exist for SDRPL patients. Symptomatic patients receive splenectomy and chemotherapy alone or sequentially. For the time being, SDRPL is an indolent but incurable disorder with a longer progression-free survival.

Most features of SDRPL were observed in this case, such as splenomegaly, moderate lymphocytosis and the specific cytology and morphology of the bone marrow and spleen, as well as the characteristic immunophenotype of the infiltrating cells. Nevertheless, SDRPL must still be distinguished from splenic marginal zone B-cell lymphoma (SMZL), hairy cell leukemia (HCL), and hairy cell leukemia-variant (HCL-v) with villous cells.

As SMZL is the most frequent small B-cell lymphoma and there is considerable overlap in the presentations of SDRPL and SMZL, it is necessary to discriminate SDRPL from SMZL. Compared with SMZL, SDRPL patients tend to be older and male [7]. In addition, the cytology and morphology of SDRPL patients are distinct. In SMZL, spleen involvement represents a biphasic marginal zone pattern of infiltration by heterogeneous cells, namely large plasmacytoid cells and small lymphoid cells with round nuclei and dense chromatin [8-10]. Furthermore, aberrant karyotyping with the 7q31 deletion is

frequent in SMZL [11]. Moreover, the IgHV1-2 segment is frequently found in SMZL, whereas the IgHV3-4 segment predominates in SDRPL [12]. SDRPL is also a more indolent disease with a longer progression-free survival than SMZL.

This patient presented with severe pancytopenia, which is usually observed in HCL and rarely occurs in SDRPL [13]. This implies that no single manifestation is truly disease-specific. It is easy to differentiate SDRPL from HCL because HCL is characterized by a distinct cytology, morphology, immunophenotype and cytogenetic profile. In HCL, leukemia cells in bone marrow have a typical "fried egg" pattern, and spleen morphology shows diffuse infiltration of the red pulp with hypoplastic white pulp and the characteristic blood lakes [14]. Mature B-cell antigens (CD20, CD22) and tumorous B-cell markers (CD11c, CD103, CD25) are readily detected by flow cytometry. The BRAF V600E mutation and Annexin A1 expression are found almost exclusively in HCL [15, 16]. However, one case, reported in 2013 by John Wiley and Sons Ltd., which was diagnosed as SDRPL while expressing Annexin A1 [5], demonstrates that no single molecule is truly disease-specific.

The differential diagnosis between SDRPL and HCL-v remains debatable due to their similar clinical-pathological presentations. Nonetheless, there are some clear differences between these two diseases. For instance, HCL-v affects older patients presenting with higher lymphocytosis. Moreover, the nucleoli of villous cells in peripheral blood are prominent in HCL-v, whereas they are small or invisible in SDRPL [17]. Additionally, HCL-v appears to harbor a lower load of immunoglobulin heavy chain variable region (IgHV) somatic hypermutation [18].

It is worth mentioning that the patient relapsed, with a CBC showing pancytopenia, 2 years after the splenectomy. Additionally, bone marrow infiltration was present in all cases available. Accordingly, we assumed that the bone marrow involvement accounts for pancytopenia, although hypersplenism matters to a degree. Nevertheless, presently, it is not possible to distinguish SDRPL from SMZL on the basis of a bone marrow biopsy alone because no significant differences are identified in terms of cytology or morphology. Overall, SDRPL is a distinct entity and requires additional study to establish its pathogenesis and diagnostic features.

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Disclosure of conflict of interest

The authors report no conflicts of interest in this work.

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