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Case Report
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A Rare Case of Splenic Diffuse Red Pulp Small B-Cell Lymphoma: One Case Report and Relevant Literature Review

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Abstract

Splenic Diffuse Red Pulp small B-cell Lymphoma (SDRPL) is an indolent lymphoma with low incidence. In the 2016 WHO edition of lymphoid neoplasms, the SDRPL is assorted into the Splenic B-cell Lymphoma/Leukemia Unclassifiable Category. However, because of its low incidence, the understanding of this disease is still insufficient. Moreover, there is no uniform standard for the treatment of this disease, and the evaluation of disease progression and prognosis is still in the exploratory stage. Here, we report a case of SDRPL and review the relevant literature in order to further explore the pathogenesis, molecular-biological characteristics and prognosis of this disease.

Keywords: CD10; Cyclin D1; SMZL; SDRPL

Case Presentation

The patient was a 58-year -old man, and the main manifestations were repeated fever. The body temperature could restore by itself. Two years ago, the serum immunoelectrophoresis showed lgM-K(+). At the same time, an abdominal ultrasound examination showed splenomegaly (intercostal space was about 4.3 cm), along with the pancytopenia. The Bone Marrow (BM) aspirate revealed abnormal proliferation of lymphocyte system; lymphocytes accounting for 86.5% of ANC (mature lymphocyte accounting for 72%) (Figure 1A). Besides, the BM biopsy showed an intra-sinusoidal and interstitial infiltration of atypical lymphoid cells highlighted by CD20 (Figure 1B), CD23 (Figure 1C), but negative for CD5 (Figure 1D), CD10 (Figure 1E), MPO, Annexin-A1, Cyclind-1 (Figure 1F), Sox-11 (Figure 1G), as well as CD123 (Figure 1H) immunostaining. Flow Cytometric (FCM) analysis demonstrated that the expressions of CD5, CD10, CD38, cyclin D1 were negative. However, about nine months before he came to our clinic, examination showed the spleen enlarged significantly. So the splenectomy was undertaken. Blood cells gradually restored after splenectomy. Besides, pathology of specimen showed growing diffusely in the red pulp sinuses and cords with obliteration of the white pulp (Figure 2A). Immunohistochemistry demonstrated that cells were positive for CD79a (Figure 2B), CD20 (Figure 2C), CD23 (Figure 2D), bcl-2, and KI-67 (15%), while negative for CD3, CD5, CD21, CD10, CD123 (Figure 2E), SOX-11, MPO, cyclin D1 (Figure 2F), mum-1, and bcl-6. The mutation of BRAFV600E and MYD88-L256P were negative.

Recently, the patient complained about spontaneous pectoralgia. The routine blood test showed lymphocytes were significantly increased. Hairy-like cells could be seen in peripheral blood smear. The Computed Tomography (CT) of thorax indicated massive left pleural effusion, and the lung tissue was compressed by 95%. FCM analysis of pleural fluid revealed that the percentage of mature B lymphocytes in the nuclear cells was 38.82%, and they expressed CD19, CD22, and CD20. Part of them expressed kappa, CD23, and CD38. But they did not express CD5 and CD103. Besides, mature cloned B lymphocytes could be found in pleural fluid. The mutation of NOTCH1 gene was synonymous mutation.

Thus, combined with the clinical features, pathology, and FCM of BM and spleen, the diagnosis was considered as SDRPL. So, the patient was given the R-CHOP (cyclophosphamide, Adriamycin, vincristine and prednisolone) regimen. After 1 cycle of chemotherapy, the temperature restored and pleural effusion gradually decreased. Besides, routine blood test showed WBC 2.25 × 10^9/L, LYM 3.1 × 10^9/L. And then, we could plan more R-CHOP regimens for later treatment.

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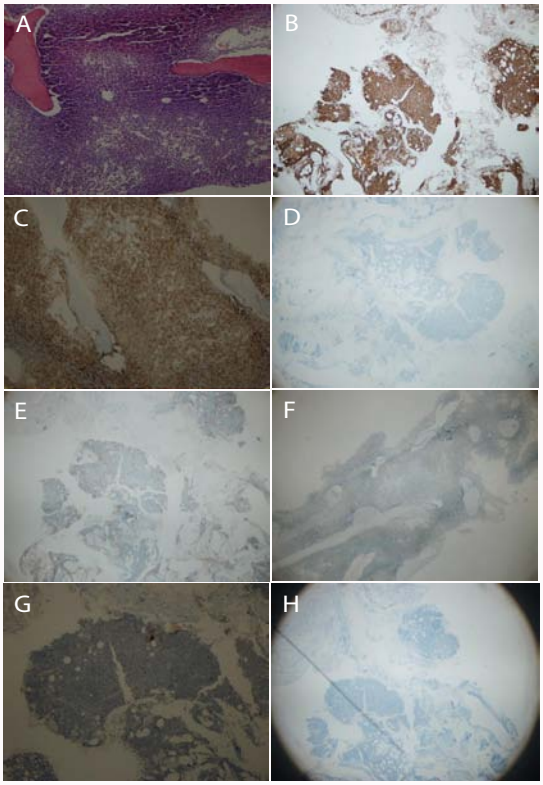

Figure 1: Bone Marrow.
(A) Small lymphocytes infiltrated in bone marrow (H&E, magnification ×10).
(B) Lymphocytes were positive for CD20.
(C) Lymphocytes were positive for CD23.
Lymphocytes were negative for
(D) CD5, (E) CD10 and (F) Cyclin D1, (G) Sox-11 and (H) CD123.

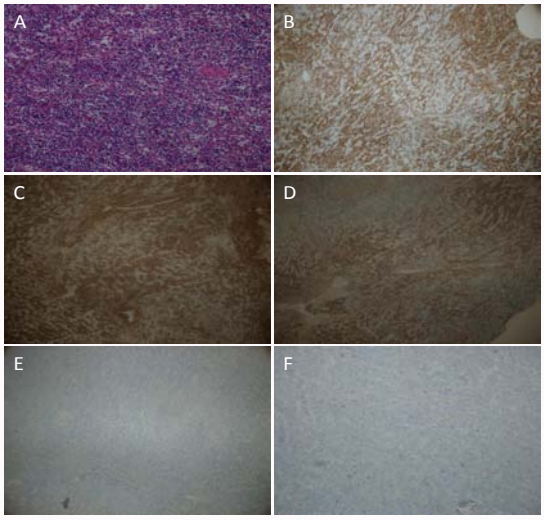

Figure 2: Splenectomy Specimen.
(A) Diffuse red pulp and sinusoidal infiltration accompanied with obliteration of the white pulp, (H&E, magnification ×100).
(B) Tumor cells were positive for CD79a, (C) CD20 and (D) CD23.
(E) Tumor cells were negative for CD123 and (F) Cyclin D1.

Discussion

SDRPL is an indolent lymphoma, which originated from the abnormality of B cells development. Its incidence is less than 1% of non-Hodgkin's lymphoma [1,2]. Based on available literature, the incidence of male is higher than female, and the median age of onset is between 65.5 and 77 years old [3]. According to the latest WHO classification criteria for lymphoid neoplasms, SDRPL is assorted into the Splenic B-cell Lymphoma/Leukemia Unclassifiable Category [4,5].

The clinical symptoms are not typical, and usually, fever and splenomegaly are the main manifestations [6]. Blood routine tests often indicate that the number of lymphocytes is increased. Also, the PB smears show the characteristic that a homogeneous infiltration of small sized cells with round or oval nuclei, as well as polar villi [1,3]. As for the pathological features of spleen, the diffuse small B cells are infiltrated in the both cord and sinusoidal, and along with reduced white pulp [7,8].

The diagnosis of SDRPL is very difficult, as a result of few features and the absence of specific molecular markers. Generally, SDRPL is easily confused with Splenic Marginal Zone Lymphoma (SMZL) and Hairy Cell Leukemia (HCL) in morphology because of their numerous circumferential hair-like villi. Then, immunophenotyping plays an important role on diagnosis and differentiation.

To data, SDRPL is strongly positive for CD20, CD22, as well as CD76. Occasionally, some tumor cells can express CD11C, CD103, IgM, IgG, and IgG+M. In most cases, CD5, CD10, CD25, CD103, CD123, Cyclin-D1, and Annexin-A1 are negative [3,9,10]. Based on the studies so far, the mutation of immunoglobulin heavy variable (IGHV) families can be used to distinguish the diseases. The frequency of IGHV3 and IGHV4 are higher in SDRPL, while IGHV1 and IGHV2 are higher in SMZL [9,11]. Some studies have shown that CD180 may be a good bio-marker for SDRPL, as the tumor cells are demonstrated to have a high expression of CD180 [11]. It also suggests that the ratio of CD200/CD180 can be useful in diagnose the SDRPL [12]. What's more, a study also suggests that Cyclin-A2, as well as Cyclin-D3 can be considered as two other bio-markers for SDRPL [9,13] but more studies are needed to confirm that. Sometimes, with the data of FCM, we may still require splenectomy for confirmation of the diagnosis. Based on the studies so far, there is little information about SDRPL related gene mutations. Occasional cases show the mutations of CCND3 and CDKN1B [9]. But whether these mutations will affect the prognosis of the disease remains unknown. Daniel Martinez has reported that the mutations of NOTCH1, TP53, and MAP2K1 can be found in SDRPL, which may associate with aggressive behavior [14]. For the patient in our report, the mutation of NOTCH1 is synonymous mutation, but it may still be a factor contributing to disease progression.

So far, there is no uniform standard for the treatment of SDRPL. At the time point of diagnosis, usually, this disease has involved the extra nodal organs. Especially, the spleen is the most frequently involved organ. So splenectomy can achieve better clinical outcomes. Reports have also shown that combine splenectomy with chemotherapy achieves better outcomes. But the chemotherapy regimen is still uncertain [3]. Cyclin-D3 plays an important role in the development of B cells. CCND3 and CDKN1B mutations are associated with the expression of Cyclin-D3. Thus, this is in accordance with the report in clinic that CCND3 and CDKN1B mutations are found in SDRPL. Cyclin-D3 can form a complex with CDK4 or CDK6 that acts on the G1/S phase of cell cycle, and the complex can rearrange the immunoglobulin heavy chain [9], which leads to the abnormality of B cells. Just like the treatment of Acute Promyelocytic Leukemia (APL),

the use of all-trans retinoic acid which aims at PML/RARα, has greatly improved the Complete Remission Rate (CR) and Disease-Free Survival Rate (DFS). From this, we may hypothesis that, in the future, there will be a potential treatment that targets the CDK4 or CDK6 to inhibit the development of tumor cells. Besides, it is also possible that therapy with agents targeting the mutations such as NOTCH1, TP53, and MAP2K1 can achieve good clinical outcomes. Then, this disease can be kept at the relatively stable stage. But more investigations on the incidence and histological features are necessary for better understanding of SDRPL and precise treatment.

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