Splenic Lymphoma with an Incidental Hemolytic Anemia: A Rare Association

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Abstract

Splenic lymphoma with villous lymphocytes (SLVL) is a rare malignancy that comprises less than 1% of lymphoid neoplasms, characterized by the presence of small atypical lymphocytes in the peripheral blood and bone marrow and splenic infiltration in the white and red pulp. It must be distinguished from other chronic lymphoproliferative disorders that present with a similar clinical and hematological profile. Here, we report a case of SLVL in a 60-year-old male with leukocytosis, massive splenomegaly, and relatively few small sized leukemic cells presenting with a Coomb's positive hemolytic anemia. It was initially diagnosed as chronic lymphocytic leukemia. The immunophenotyping studies and marrow examination indicated a diagnosis of SLVL. This case highlights the diagnostic pitfalls associated with this rare disorder.

INTRODUCTION

Chronic lymphoproliferative disorders (CLPD) are characterized by the accumulation of mature–appearing lymphoid cells in the peripheral blood, marrow, lymph nodes, and spleen. There are a handful of these neoplasms which are close mimickers morphologically and can lead to erroneous diagnosis. Few of them are also associated with other hematological manifestations such as immune hemolytic anemia and immune-mediated thrombocytopenia. Splenic lymphoma with villous lymphocytes (SLVL), although relatively uncommon as compared with its other neoplastic counterparts, such as chronic lymphocytic leukemia (CLL), is perhaps under-diagnosed due to lack of awareness about its features and its associations. We encountered one such confounding case of SLVL which was initially overlooked as CLL only to be revealed later by ancillary studies.

CASE REPORT

A 60-year-old male was referred to our hospital with symptoms of fatigue and significant weight loss. On systemic examination, the patient was pale and mildly icteric. On systemic examination, a splenomegaly of 14 cm was palpable below the left costal margin. The liver was mildly enlarged. Lymphadenopathy was absent. The working clinical diagnosis was amyeloproliferative neoplasm. The laboratory investigation revealed a bicytopenia: Hemoglobin (Hb) of 8.3 g/dl, platelet count of 53 × 10³/UL. The total white blood cell count was increased (33.1 × 10³/UL). The peripheral blood film examination revealed an immune hemolytic morphology of red blood cells. The differential count showed 68% lymphoid cells. Morphologically, the atypical lymphoid cells were small-sized with a moderate amount of cytoplasm. The nuclei were round with a condensed chromatin. Occasional smudge cells were also seen, although not numerous. A provisional diagnosis of CLPD, suggestive of CLL was given on the smear.

The Coomb’s test was weakly positive, thus confirming the hemolytic anemia. The bone marrow aspirates and subsequent trephine biopsy examined showed interstitial infiltration by small lymphoid cells. Few of the cells in the peripheral smear and aspirate smears showed small subtle villous projections on the cytoplasmic surface (Figure 1). Flow cytometric immunophenotyping was performed on peripheral blood, and the lymphoid cells were gated using CD19 based on their forward and side scatter characteristics and they constituted 67.02% of the total cells. The CD19 gated cells were negative for CD3, CD5, CD10, CD23, CD103, and CD25. The cells were positive for CD20 and kappa Ig (Figure 2). Cytogenetic studies showed normal male karyotype.

Keywords: Hemolytic anemia, Lymphocytes, Splenomegaly
Based on the clinical features, morphological and immunophenotyping characteristics, a diagnosis of SLVL was rendered. The patient received two cycles of chemotherapy with bendamustine and rituximab. The corresponding blood film examination showed an improvement in the Hb and platelet count. At the time of writing this article, the counts have remained stable.

**DISCUSSION**

SLVL - a low-grade B-cell lymphoma first described by Neiman et al. in 1979. They reported a series of 10 cases of splenic lymphomas that mimicked hairy cell leukemia. These findings were corroborated by Melo et al. who reported a series of 22 patients and coined the term SLVL. The recent World Health Organization classification in 2008 has incorporated SLVL as the leukemic form of splenic marginal zone lymphoma.

Though eponymously associated with the spleen, the peripheral blood and bone marrow can be involved frequently. This spill-over into the circulation can simulate many other small lymphoid neoplasms which can lead to a diagnostic dilemma. The amount of circulating cells can sometimes be scant, which can evade detection by a pathologist. In obvious peripheral blood involvement, numerous mature B-lymphocytes with pale cytoplasm and villous projections can easily be recognized. In the present case, lymphoid cells were small-sized with the moderate amount of cytoplasm and condensed chromatin. In retrospect, the villous projections were seen only in the small percentage of cells. These cells were overlooked at the time of initial presentation. A very high lymphocytosis and the presence of relatively few numbers of cells with inconspicuous nucleoli and subtle surface projections characteristic of SLVL led to initial misdiagnosis of CLL.

Occasional smudge cells were also seen which misled us into a diagnosis of CLL. Such instances have been mentioned in literature as well. Furthermore, the simultaneous existence of Coomb’s positive hemolytic anemia also favored the possibility of a CLL. Autoimmune phenomena in coalition with SLVL have been described by workers such as Bonichon et al. and Gale et al. In SLVL, the number of villous lymphocytes vary from case to case, and if they constitute less than 25% of the lymphocytes as observed in the present case, the diagnosis may be difficult to establish on morphology alone. All these factors ultimately led us to overlook SLVL.

In the case of marrow involvement, different types of infiltration have been described: Interstitial, nodular,
paratrabecular, and even intrasinusoidal.\textsuperscript{7} However, intrasinusoidal infiltration is considered to be the most specific for SLVL.\textsuperscript{8} Different patterns of marrow infiltration have been linked to different phases of the disease; in early phases, the intrasinusoidal pattern predominates, whereas in advanced cases it tends to diminish and nodular formations tend to increase.\textsuperscript{8} In the present case, an interstitial pattern of infiltration was observed.

Looking back, there were clues which suggested a diagnosis of SLVL in this case. The absolute lymphoid cell count was 22.108 $\times 10^9$/cu.mm in the present case. This was in accordance with SLVL which is usually associated with moderate lymphocytosis.\textsuperscript{2} The characteristic checkerboard pattern of chromatin clumping observed in lymphoid cells of CLL was conspicuously absent in this case. The lymphoid cells with small villous projections were seen in a small albeit significant percentage of lymphoid cells. Furthermore, the smudge cells can be seen in other low-grade B-cell neoplasms apart from CLL.

Immunophenotyping by flow cytometric analysis remains a confirmatory test in SLVL. Positivity for CD20, CD45RA, CD45RB, CD79a, IgM, and bcl-2 and negativity for CD43, CD10, CD23, CD5, bcl-6, annexin A1, and cyclin D1 are constantly observed.\textsuperscript{3,9} Occasional positivity for CD5 has been reported in a minority of patients.\textsuperscript{10} The immunophenotyping in this case was in concordance with the above panel.

The differential diagnoses entertained with SLVL are the usual suspects: Hairy cell leukemia (HCL), B-cell CLL, follicular lymphoma (FL), and mantle cell lymphoma (MCL). CLL shows a highly condensed chromatin and inconspicuous nucleolus admixed with larger prolymphocytes showing CD23+, CD5+, and a lower expression of CD20. HCL produces a patchy infiltration punctuated by extravasated red blood cells and a progressive replacement of normal hematopoietic elements. Reticulin fibrosis is increased in HCL accounting for higher tendency of a dry tap. Besides, HCL cells are CD23+, CD103+ and annexin A1+. MCL is associated with a lymphadenopathy and the bone marrow shows an interstitial, diffuse, or nodular infiltration pattern. An intrasinusoidal component is not observed in MCL. MCL cells are characteristically CD5+, CD43+, and cyclin D1+. FL also present with a peripheral lymphadenopathy but are CD10+ and bcl-6+.

CONCLUSION

The present case demonstrates the diagnostic challenges in a case of CLPD. The subtle morphological features of SLVL may be easily overlooked. The morphology of lymphoid cells and marrow infiltration patterns may help to narrow down the differential diagnoses. However, a complete immunophenotype profile remains imperative for the diagnosis of SLVL as the treatment protocols and prognosis differ from other lymphomas.

REFERENCES