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Case Report

Splenic lymphoma with villous lymphocytes

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ABSTRACT

Splenic lymphoma with villous lymphocytes (SLVL) is a rare disorder that comprises less than 1% of lymphoid neoplasms. It is the leukemic counterpart of splenic marginal zone lymphoma (SMZL) and is characterized by splenomegaly, often with no lymphadenopathy, moderate lymphocytosis and villous lymphocytes on peripheral blood smear. Here, we report a case of SLVL in a 56-year-old male with very high leukocyte counts, massive splenomegaly and relatively few leukemic cells with subtle villous projections on the surface. This disorder is often confused with other chronic lymphoproliferative disorders, especially chronic lymphocytic leukemia (CLL) and hairy cell leukemia and should be differentiated from them. We are reporting this case to highlight the diagnostic pitfalls associated with this disorder.

KEY WORDS: Chronic lymphoproliferative disorders, leukocytosis, splenic lymphoma with villous lymphocytes, splenic marginal zone lymphoma

INTRODUCTION

Splenic lymphoma with villous lymphocytes (SLVL), although relatively uncommon as compared with other chronic lymphoproliferative disorders (CLPD), is perhaps under-diagnosed due to lack of awareness and paucity of immunophenotyping facilities. It must be distinguished from other B-cell lymphoproliferative disorders that present with peripheral blood lymphocytosis and splenomegaly. There is considerable overlap of clinical and morphological features between the various CLPD. A precise pathological diagnosis is imperative in this group of disorders as the treatment modalities differ. Here, we report a case of SLVL that was initially misdiagnosed as chronic lymphocytic leukemia (CLL) based on high total leukocyte counts and light microscopic studies.

CASE HISTORY

A 56-year-old male was referred to our center as a case of CLL in November 2003. On physical examination, the patient had splenomegaly of 20 cm and hepatomegaly of 2 cm below the costal margin. Peripheral lymphadenopathy was absent. Laboratory investigations revealed a hemoglobin of 3.3 g/dl, platelet count of 22×10^9/l, white blood cell count (WBC) of 80×10^9/l and an absolute lymphocyte count of 78×10^9/l. Morphologically, the atypical lymphoid cells were larger than the small lymphocytes with moderate amount of cytoplasm. The nuclei were round with condensed chromatin. The chromatin clumping was not as marked as observed in CLL cells. Small indistinct nucleoli were observed in 5% of cells. Fine villous surface projections mostly concentrated at one or both the poles and were sometimes observed to be irregularly distributed in 15% of the lymphoid cells [Figure 1]. The leukemic cells were negative for tartrate-resistant acid phosphatase. Flow cytometric immunophenotyping was performed on peripheral blood, and the lymphoid cells were gated based on their forward and side scatter characteristics and they constituted 49.7% of the total cells. Of these lymphocytes, 46.2% lymphoid cells were B-lymphoid cells expressing CD19 and 42.1% lymphoid cells were T-lymphoid cells expressing CD5. Lymphoid cells with dual expression of CD19 and CD5 were not observed and thus the possibility of CD5-positive B-lymphoid disorder such as CLL and mantle cell lymphoma (MCL) was ruled out. The other markers expressed by the gated lymphoid cells were CD20, CD25, CD38 and FMC-7. The monoclonality for kappa light chains with moderately strong expression was observed. The lymphoid cells were negative for CD10, CD23 and CD103 [Figure 2]. Cytogenetic studies showed normal male karyotype.

Based on the clinical, morphological and immunophenotypic characteristics, a diagnosis of SLVL was made. Patient received pneumococcal and Hemophilus influenzae vaccination and underwent splenectomy in February 2004. A diffuse infiltration of atypical lymphoid cells was observed both in the white and red pulp. Immunohistochemical studies on splenic tissue were negative for cyclin D1 and CD43. Postoperative WBC counts were 120×10^9/l with an absolute lymphocyte count of 114×10^9l. Patient received six cycles of chemotherapy (CHOP) after which his hemogram showed a hemoglobin level of 8.7g/dl, platelet count of 195×10^9/l, and WBC count of 12.4×10^9/l with 65% lymphocytes.

DISCUSSION

Splenic lymphoma with villous lymphocytes - a low grade B-cell lymphoma first described by Neiman *et al.* - was characterized in detail by Melo *et al.* who reported a series of 22 patients and introduced the term SLVL.[1,2] The recent World Health Organization classification has incorporated SLVL as the leukemic form of SMZL.[3]

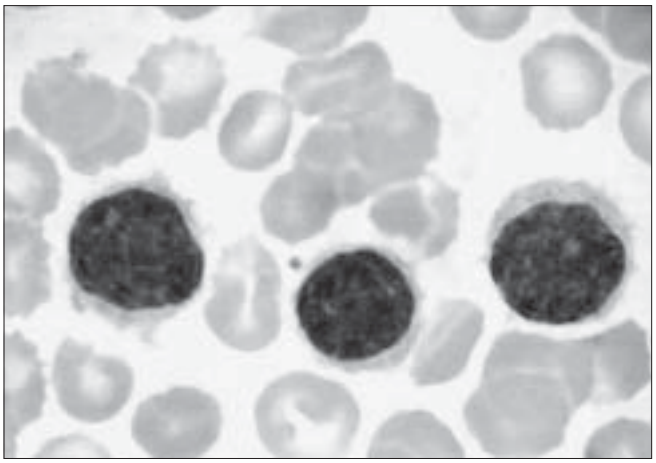

Figure 1: Lymphoid cells showing condensed chromatin, inconspicuous nucleoli and villous projections on cell surface (Leishman, ×1000)

Patients with SLVL usually present with nonspecific symptoms related to anemia or discomfort in the left hypochondrium due to splenomegaly. This is usually associated with a moderate lymphocytosis. Morphologically, the SLVL cells are slightly larger than small lymphocytes with condensed chromatin, inconspicuous nucleoli, moderate amount of cytoplasm and fine villous projections on the cell surface.

In the present case, an initial diagnosis of CLL was made due to the presence of absolute lymphocytosis of greater than 10×10^9l. This was in accordance with the criteria of International workshop on CLL.[4] The characteristic morphological features of SLVL were present only in 15% of the lymphoid cells. These cells were overlooked at the time of initial presentation. A very high lymphocytosis and presence of relatively few number of cells with inconspicuous nucleoli and subtle surface projections characteristic of SLVL led to initial misdiagnosis.

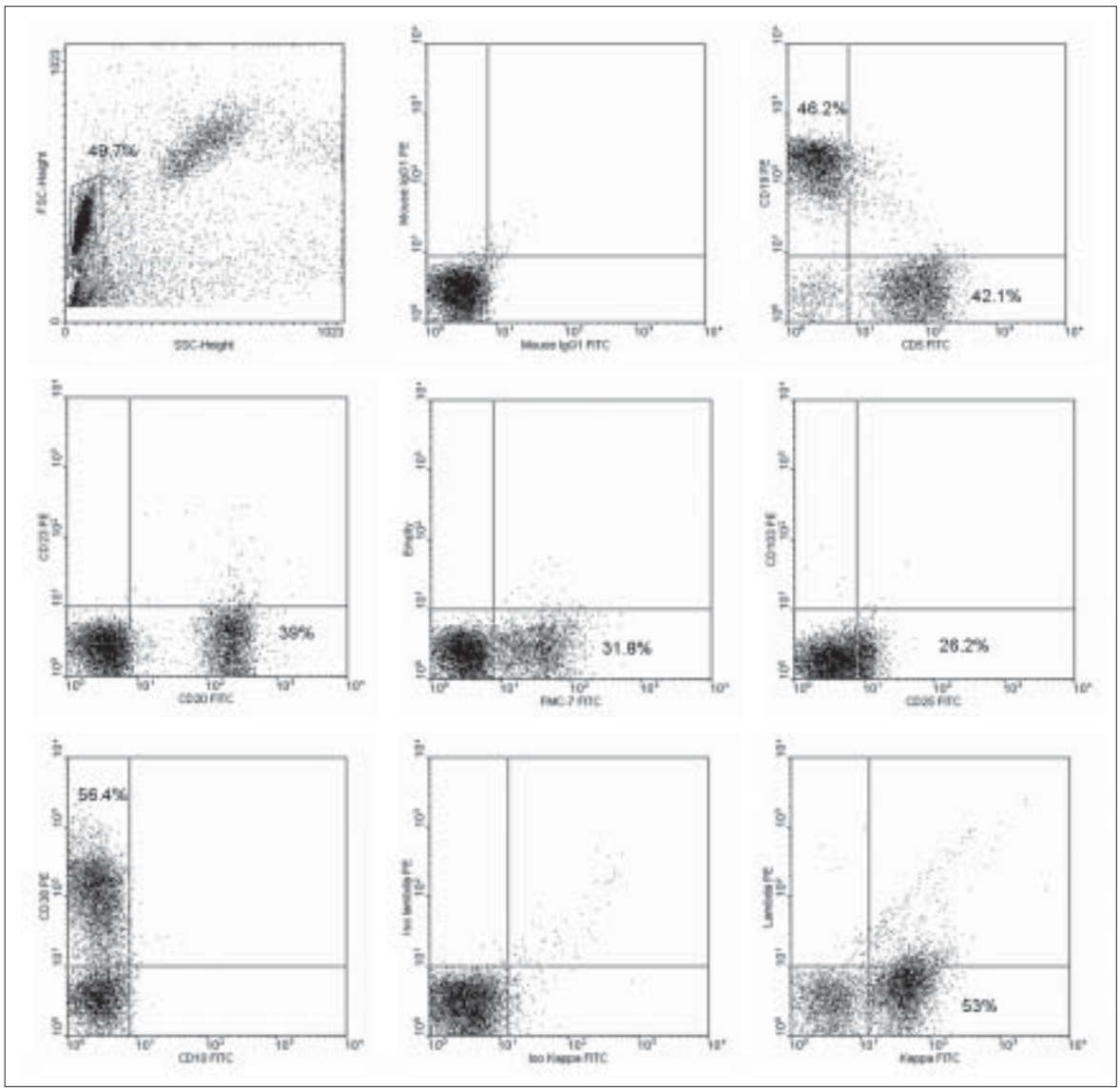

Figure 2: Dot plots showing immunoreactivity pattern of lymphoid cells: The lymphoid cells are positive for CD19, CD20, CD25, CD38, FMC-7 and monoclonal for κ light chain; lymphoid cells with dual expression of CD5 and CD19 are not seen

Table 1: Comparison of morphological features in various chronic lymphoproliferative disorders

	Chromatin condensation	*Nucleoli*	*Cytoplasm*	*Cleaved cells*	*Surface villi*	*TRAP*
CLL	Marked	–	Minimal	–	–	–
PLL	Moderate	+	Moderate	–	–	–
HCL	Moderate	–	Moderate	–	+, Circumferential	+
FL	Moderate	–	Minimal	+	–	–
MCL	Moderate	–	Variable	+/–	–	–
SLVL	Moderate	+, Inconspicuous	Moderate	–	+, Polar	–

+, present; –, absent; +/–, may be present; CLL, chronic lymphocytic leukemia; PLL, prolymphocytic leukemia; HCL, hairy cell leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; SLVL, splenic lymphoma with villous lymphocytes; TRAP, tartrate resistant acid phosphatase

Table 2: Comparison of immunophenotypic features of various chronic lymphoproliferative disorders

	CD5	*CD19, CD20*	*CD23*	*FMC-7*	*CD10*	*CD25*	*CD103*	*Surface membrane-bound immunoglobulin (SmIg)*
CLL	++	++	++	–/+	–	–	–	Weak
PLL	–/+	++	–	++	–/+	–	–	Strong
HCL	–	++	–	++	–	++	++	Strong to moderate
FL	_	++	–/+	++	+	–	–	Strong
MCL	++	++	–/+	+	–/+	–	–	Moderate
SLVL	–	++	–/+	–/+	–	–/+	–	Strong

+ - expressed; ++ - strongly expressed; – - not expressed; +/– - may be expressed, CLL - chronic lymphocytic leukemia; PLL - prolymphocytic leukemia; HCL - hairy cell leukemia; FL - follicular lymphoma; MCL - mantle cell lymphoma; SLVL - splenic lymphoma with villous lymphocytes

High peripheral lymphocytosis, although reported, is unusual in SLVL; this is usually associated with moderate lymphocytosis.[2] The characteristic checkerboard pattern of chromatin clumping observed in lymphoid cells of CLL was conspicuously absent in this case. The paucity of such lymphoid cells in a case should alert the pathologist to the possibility of a low-grade CLPD other than CLL and warrant a careful morphological examination. 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.[5] Care should be taken to correctly identify the villous artifact on peripheral blood smears due to smearing and differentiate it from ruffled cytoplasmic borders of villous lymphocytes.

Other CLPD such as prolymphocytic leukemia (PLL), hairy cell leukemia (HCL), leukemic phase of follicular and mantle cell lymphoma (MCL) may present with overlapping clinical and morphological features and should be considered in the differential diagnosis of SLVL [Table 1]. Cells in PLL and HCL have moderate to abundant amount of cytoplasm and the latter has significant villous projections on the surface. The predominant population of cleaved cells characterizes leukemic form of follicular lymphoma (FL). The differentiation from MCL cells may not be possible on morphology alone and immunophenotyping is required.

Immunophenotypically, SLVL cells have a variable profile of antigen expression. No surface marker in isolation is characteristic of SLVL, and therefore, a complete panel of markers is required to differentiate it from other lymphoproliferative disorders.[6] In the present case, the absence of CD5, CD23 on peripheral blood and cyclin D1 on splenic tissue ruled out a diagnosis of CLL and MCL. CD103 and CD10 were helpful in ruling out HCL and leukemic phase of FL. Immunological markers useful in differentiating various CLPD have been tabulated [Table 2].

The present case emphasizes the importance of careful morphological evaluation and awareness of the subtle morphological features of SLVL. Cases of low-grade CLPD with subtle morphological variations should be further evaluated by immunophenotyping.

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