

Case Reports

SPLENIC LYMPHOMA WITH VILLOUS LYMPHOCYTES: REPORT OF THREE CASES

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Splenic lymphoma with villous lymphocytes (SLVL) is a recently recognized entity among chronic B lymphoproliferative disorders. It has a distinct clinical, morphological and immunophenotypic pattern and was previously described under a variety of designations. SLVL can be misdiagnosed as chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), or hairy cell leukemia (HCL). Characteristically, these cells are CD5-, CD10-, CD23-, CD25-, HC2-, FMC7+, CD19+, CD22+ and strongly positive surface Ig (SmIg). Patients with SLVL are elderly (usually males) with splenomegaly and lymphocytosis ($<100 \times 10^9/L$), with many villous lymphocytes, IgM monoclonal gammopathy in some, and usually have a benign course. We describe three cases of SLVL from the Eastern Province of Saudi Arabia. To our knowledge, this is the first well-documented report of SLVL from Saudi Arabia.

Case Reports

Case 1

A 75-year-old Saudi male was first admitted to our hospital eight years ago. At that time, he had ischemic heart disease with inferior wall myocardial infarction and NIDDM. He had no splenomegaly and his CBC was normal. The patient was also known to have obstructive uropathy with hydronephrosis due to ureteric calculi, and had had an operation for this two years before that time. Four years ago, splenomegaly and lymphocytosis were noticed (Table 1), for which a diagnosis of CLL was made. Approximately three years ago, one of the authors (MIQ) noticed some villous lymphocytes in his blood film, and the patient was recalled for examination and evaluation. Examination showed a huge splenomegaly crossing the umbilicus. No lymphadenopathy was present. Ultrasonography showed the spleen was 20 cm long, the splenic vein was 1.4 cm, and there was bilateral

FIGURE 1A. Lymphocytes of varied morphology in blood (MGG stain, 1000x).

FIGURE 1B. A lymphocyte with polar villi (MGG stain, 1000x).

hydronephrosis. Hemogram findings are shown in Table 1. The blood film showed varied forms of lymphoid cells. Some were large with abundant pale-blue cytoplasm. The nuclei had clumped chromatin and prominent nucleolus in some. Some lymphocytes were binucleated and an occasional one was plasmacytoid. Several cells had fuzzy cytoplasm. Lobulated nucleus was seen in a few cells (Figure 1A). There was another population of lymphoid cells which were comparatively small to medium in size but

TABLE 1. Hemogram findings in 3 cases.

Parameters	Case 1		Case 2	Case 3	
	4/11/16H	9/2/17H	4/3/18H	22/3/18H	5/2/19H
Hb (g/dL)	12.2	10.7	7.8	8.1	6.4
RBC $\times 10^{12}/dL$	4.89	4.38	2.9	3.19	2.08
HCT (ratio)	0.376	0.34	0.233	0.258	0.186
Platelets $\times 10^9/L$	190	165	140	148	16
WBC $\times 10^9/L$	24.19	20.86	21.79	49.39	1.3
Differentials %					
Neutrophils	8	15	1	9	8.5
Lymphoid cells	92	82	99	90	89.5
Eosinophils	–	3	–	1	2.0
Villous lymphocytes	?	?	13	80	8

TABLE 2. Immunophenotype (FAC scan) results.

Parameters	Case 1	Case 2	Case 3
	CD3	11	12
CD5	10	13	51
CD7	11	10	48
CD10	0	0	0
CD13	2	10	13
CD14	–	3	0
CD19	88	89	54
CD20	91	89	–
CD22	89	89	50
CD23	18	0	34
CD25	0	0	1
CD33	3	0	1
CD34	5	0	0
Kappa	5	0	35 (moderate)
Lambda	35 (moderate)	89 (strong)	1

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DR	93	89	–
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TABLE 3. Bone marrow aspiration and trephine biopsy findings.

Case 1	Hypercellular; diffuse involvement; 86% lymphocytes; morphologically heterogeneous: small, medium and large ones; some plasmacytoid; clumped nuclear chromatin; nucleoli indistinct to prominent; villous forms ~10%; around 10% lymphocytes had PAS-positive fine granules; all lymphoid cells were acid phosphatase positive and 75% were weakly tartrate resistant; no fibrosis; high iron stores (4+).
Case 2	Hypercellular; nodular + diffuse involvement (Fig. 2A); 90% lymphocytes; morphologically heterogeneous—large and small ones; some plasmacytoid; clumped nuclear chromatin; indistinct nucleoli; villous lymphocytes ~80%; majority of lymphoid cells had PAS-positive fine granules; majority of lymphoid cells were acid phosphatase positive but only 5% were weakly tartrate resistant; no fibrosis (Fig. 2B).
Case 3	Hypercellular; nodular + diffuse involvement; 94% lymphocytes; morphologically heterogeneous: large and small ones; clumped nuclear chromatin; majority indistinct nucleoli but some have 1-2; villous forms ~60%; less than 5% lymphoid cells had PAS-positive fine granules; all lymphocytes were acid phosphatase positive but only 10% were weakly tartrate resistant; no fibrosis.

had short villi. These villi were either at one side (polar) (Figure 1B), or were located throughout the cell border. The percentage of such cells varied in different slides and on different occasions, but were between 10% and 30%. Some of the lymphoid cells were normal-looking small lymphocytes. A few smudge cells were also seen. The results of immunophenotype of blood lymphocytes using Becton Dickinson FAC SCAN are shown in Table 2. Serum protein electrophoresis showed no monoclonal gammopathy. Serum IgG/M/A were normal. Serum creatinine was slightly raised (1.99 mg/dL) and uric acid was 8.6 mg/dL. Bone marrow findings are shown in Table 3. The patient has shown a progression of the disease over three years of follow-up, and splenectomy is being considered.

Case 2

A 70-year-old Saudi male farmer had been complaining of recurring fever for the previous five years. He was being treated by a local pharmacist with antibiotics. Four years ago, a traditional “healer” told the patient that he had an enlarged spleen, and so cauterized the affected area. On examination at the hospital, the patient’s spleen was 12 cm below the costal margin. His liver span was 13 cm, and he had small shotty lymph nodes in the anterior and posterior cervical regions, the largest of which was 0.5 cm. Hemogram results are shown in Table 1. Blood film showed the heterogeneous character of lymphoid cells, some of which were large with plenty of cytoplasm. The nucleolus present in some nuclei was indistinct. Others were small to medium-sized lymphocytes with little cytoplasm. About 80% of lymphocytes, especially the small ones, had both polar and circumferential villi. The immune profile of the blood lymphocytes is shown in Table 2. Serum protein electrophoresis was normal. Bone marrow findings are

shown in Table 3. Other laboratory investigations were normal. The patient’s condition was stable during one year of follow-up.

Case 3

An 80-year-old Saudi female was admitted to the emergency room with severe pallor, fever, sore throat and dry cough. Her liver was 2 cm below the costal margin, and the spleen was not palpable but was enlarged on ultrasonography. Gallstones were also found, and the patient had right lower zone pneumonia. Hemogram findings are as shown in Table 1. The lymphocytes present were varied in morphology and between 5% and 15% showed short villi on different occasions. Serum protein electrophoresis was normal, but serum calcium was slightly low (7.74 mg/dL). The bone marrow findings are shown in Table 3. The immunophenotype results on bone marrow sample are shown in Table 2. The patient died nine months after the diagnosis of SLVL due to pneumonia and septicemia.

Discussion

The presence of villous lymphocytes in the blood film of these three elderly patients, with huge splenomegaly and moderate lymphocytosis in two of them, prompted us to suggest the diagnosis of SLVL. The bone marrow

FIGURE 2A. Trephine marrow biopsy section showing an ill-defined lymphoid nodule at left upper central area. There is also diffuse lymphocyte infiltration (H&E stain, 200x).

FIGURE 2B. Trephine marrow biopsy section stained for reticulin with silver impregnation method. Section includes border area of nodule shown in A at upper right central area. There is no reticulin condensation (fibrosis) (400x).

TABLE 4. Comparison of immunophenotype results with two series reported in the literature.

	Present 3 cases	Matutes et al. ² % positive (100 cases)	Troussard et al. ³ % positive (100 cases)
CD5	1	19	20
CD10	0	30	3
CD19	3	100	100
CD20	3	100	100
CD22	3	95	87
CD23	1 (weak)	31	17
CD25	0	25	5
DR	3	100	100
Kappa	1	60	50
Lambda	2	40	50
CD11c	–	47	54
HC2	–	9	–
FMC7	–	89	–

involvement was also distinct and different from HCL. The immunophenotype was classical of SLVL (Table 2).

Expression of SmIg was moderate in two cases, however, weak to moderate SmIg has been described in 42% of cases of SLVL.² Negative CD23, CD25 and CD5 (in two cases), with strongly positive CD19, CD20 and CD22, were all in favor of SLVL and against CLL, PLL and HCL. The immunophenotype in our three cases was in accordance with two large series reported in the literature (Table 4). Initially, monoclonal gammopathy (especially IgM) was thought to be classical, but now it is reported positive in as low as 28% of the cases.³ TRAP positivity is classically seen in HCL, but weak positivity has also been reported in some SLVL patients.^{3,4}

The diagnosis of SLVL should be considered in all cases of elderly patients with huge splenomegaly with lymphocytosis. However, the absence of lymphocytosis has been reported in up to 24% cases.³ A careful morphology is the most useful basis for the diagnosis of SLVL.³ Villous lymphocytes range between 5% and 90% in blood.^{1,3} Finding of villous lymphocytes is particularly difficult in cases with absence of lymphocytosis. The diagnosis of SLVL may be missed in these cases, and may be misdiagnosed as any of the other chronic lymphoproliferative disorders.^{1,3} However, bone marrow examination complemented by immunophenotyping can identify such cases.³ This approach was helpful in our third case. However, one should remember that the diagnosis of SLVL should not be made only on the basis of morphology, but should be confirmed by immunophenotyping. Morphological heterogeneity of lymphocytes is well described in SLVL¹ and this was a marked feature in our first case. Splenomegaly can be absent in up to 24% of cases of SLVL. Anemia, thrombocytopenia and neutropenia can be seen in 5%-10% of cases.^{1,3} Pancytopenia with absence of palpable spleen was a marked feature in our third case. Neutropenia became a feature in our first case as the disease progressed.

Characterization and identification of SLVL cases is important, as the course of the disease and the treatment modalities are different from other chronic B-cell disorders.^{2,3} Various scoring systems based on immune profile have been suggested to distinguish between B-cell chronic leukemias and lymphomas.⁵⁻⁸ The histology of the spleen in SLVL is also characteristic.⁹

There is a paucity of reports of SLVL from the Middle East. Only a single report of two cases from Kuwait has previously been published.¹⁰ We believe that this report of three cases of SLVL is the first from Saudi Arabia.

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