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Splenic Lymphoma with Villus Lymphocytes - An Uncommon Cause for Lymphocytosis

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ABSTRACT

We describe the clinical and laboratory features of four patients who presented with mild to moderate lymphocytosis but with no peripheral lymphadenopathy. These patients in the past, would have been classified as chronic lymphocytic leukaemia (CLL). However, it is now realised that chronic lymphoproliferative disorders are very heterogeneous and the clinical and laboratory features of our patients would support a diagnosis of splenic lymphoma with villus lymphocytes (SLVL) with characteristic morphological features. SLVL usually runs a benign clinical course but symptoms related to splenomegaly or hypersplenism may be a problem. Splenectomy is considered the treatment of choice in these patients. Two of our patients had splenectomy and the other two patients are on regular follow-up without any specific treatment. It is therefore important to recognise this uncommon condition and also to differentiate it from CLL.

Keywords: lymphocytosis, chronic lymphocytic leukaemia, splenic lymphoma with villus lymphocytes

INTRODUCTION

When an adult patient presents with persistent lymphocytosis, a chronic lymphoproliferative disorder is the most likely diagnosis. These disorders are the most common form of haematological malignancies in the western world but are uncommon in Asia[1-8]. A recent study from Hong Kong has shown that these disorders can no longer be considered rare in Asia[9].

Most of these disorders in the past were grouped under chronic lymphocytic leukaemia but it is realised now that chronic lymphoproliferative disorder is very heterogeneous with varying clinical features and prognosis. Here we present four cases of splenic lymphoma with villus lymphocytes (SLVL), presented to our hospital within the last 2 years. This is an uncommon type of chronic lymphoproliferative disorder but with characteristic clinical, morphological and immunophenotypic features which help to differentiate this disorder from chronic lymphocytic leukaemia[10-12].

CASE 1

A 67-year-old Jewish lady presented to the orthopaedic department with neck pain for 3 months. Otherwise she was well and did not have any fever, weight loss or night sweating. On examination, there was no lymphadenopathy or hepatomegaly, but the spleen was enlarged, almost reaching the umbilicus. Full blood examination (FBC) showed that the white cell count (WBC) was 9.2 x 10^9/L, haemoglobin 12.3 gm/dL and platelets 91 x 10^9/L. The absolute neutrophil count was 3.7 x 10^9/L and she had an absolute lymphocytosis of 5.1 x 10^9/L. Some of the lymphocytes morphologically resembled mature lymphocytes while other cells were larger with moderate amount of cytoplasm. Few cells had single prominent nucleolus. There were no typical hairy cells but many lymphocytes had fine villus projections. The bone marrow showed normal development of all three cell lines but there was diffuse infiltration by lymphoid cells. The trephine biopsy did not show the typical clear zone pattern seen in hairy cell leukaemia. The other laboratory and the immunophenotypic features are given in Table I. The patient went back to Israel and a splenectomy was done there.

CASE 2

A 61-year-old Chinese man presented with a history of lethargy for a period of 3 to 4 months. He has had carcinoma of the thyroid 12 years previously and was treated by total thyroidectomy, and has been on thyroxine replacement since then. There was no history of fever, weight loss or night sweating. Two years prior to this appointment, he was told that he had lymphocytosis on routine FBC examination. On examination, he was not pale or jaundiced and there was no lymphadenopathy. He had an enlarged spleen which was just palpable below the left costal margin. A CT scan of the abdomen confirmed the splenomegaly but there was no para aortic lymphadenopathy. His WBC was 18.9 x 10^9/L, haemolgobin 12.6 gm/dL and the platelet count 234 x 1 0^9/L with the absolute neutrophil count of 4.0 x 1 0^9/L and lymphocyte count of 12 x 10^9/L. The morphology of the lymphocytes were not typical of chronic lymphocytic leukaemia. The lymphoid cells were larger than the small lymphocytes and had moderate amount of cytoplasm and some cells with a single prominent nucleolus. There were no obvious hairy cells but some lymphocytes had fine hairy projections mainly on one pole of the cell. The bone marrow biopsy showed diffuse infiltration of the marrow by lymphoid cells but lacked the typical clear zone pattern of hairy cell leukaemia. The other

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Table I - Summary of the laboratory features of the cases

	Case 1	Case 2	Case 3	Case 4
Race	Jewish	Chinese	Chinese	Chinese
Sex	female	male	male	male
Age	67	61	59	53
WBC (10^9/L)	9.2	18.9	12.1	20.7
Hb (g/dL)	12.3	12.6	12.7	12.3
Platelets (10^9/L)	91	234	234	102
Neutrophils (10^9/L)	3.7	4.0	3.0	2.7
Lymphocytes (10^9/L)	5.1	12.0	8.4	17.0
LDH U/L (300-650)	753	640	451	888
Paraprotein (g/L)	Absent	4.8	Absent	Absent
Acid phosphate (tartrate resistant)	Weakly positive	Weakly positive	Negative	Negative
Cytogenetics	Normal female 46XX	Not done	Not done	Normal male 46XY

Table II - Immunophenotypic features of the 4 cases

	Case 1	Case 2	Case 3	Case 4
CD2	-	-	-	-
CD3	-	-	-	-
CD5	-	+	+	+
CD19	+	+	+	+
CD20	+	+	+	+
CD11c	-	-	-	-

\+ indicates positive in >20% of cells
\- indicates negative

laboratory and immunophenotypic features are given in Table I.

He was not given any specific treatment and he is being followed regularly for the last 2 years. During this period, the WBC has fluctuated between 15 - 30 x 10^9/L .

CASE 3

A 59-year-old Chinese man went to his general practitioner for a regular check-up, and routine FBC showed that he had absolute lymphocytosis. He was generally well and did not have any constitutional symptoms. He has been on treatment for hypertension with nifedipine for many years.

On examination, he was not pale and there was no lymphadenopathy or hepatosplenomegaly. His FBC showed that WBC was 12.1 x 10^9/L, haemoglobin 12.7 gm/dL, platelet count was 224 x 10^9/L with an absolute neutrophil count of 3.0 x 10^9/L and a lymphocyte count of 8.4 x 10^9/L. The lymphoid cells were morphologically larger than the mature lymphocytes and had moderate amount of cytoplasm. Occasional cells had a single nucleolus and a few had fine hairy projections on one pole of the cell. The other laboratory and immunophenotypic features are given in Table I. He was not given any specific therapy and is being followed-up regularly.

CASE 4

A 53-year-old Chinese man presented to the hospital with pain in his left flank for 2 weeks. There was no history of fever, weight loss or night sweating. On examination, he was not pale or jaundiced and there was no lymphadenopathy or hepatosplenomegaly. However, the spleen was enlarged 15 cm below the left costal margin. CT scan of the abdomen confirmed the enlargement of the spleen but there was no significant lymphadenopathy. The liver function tests were within normal limits.

The FBC showed that the WBC was 20.7 x 10^9/L, haemoglobin 12.3 gm/dL and platelets was 102 x 10^9/L. The absolute neutrophil count was 2.7 x 10^9/L and the lymphocyte count was 17 x 10^9/L. The lymphocytes were morphologically larger than the small lymphocytes and had moderate amount of cytoplasm and some with single nucleolus. Some cells had fine hairy projections mainly at one pole of the cell. The bone marrow biopsy showed diffuse infiltration of the marrow by lymphoid cells but lacked the typical clear zone pattern of hairy cell leukaemia. Further laboratory and immunophenotypic features are given in Table I.

A splenectomy was done and the spleen weighed 1.5 kg at surgery. The section of the spleen showed prominent white pulp. The white pulp was replaced by intermediate sized lymphocytes with rounded nuclei and moderate amount of cytoplasm, and the infiltration extended into the red pulp. The patient had an uneventful recovery and post-splenectomy FBC showed a WBC of 18.2 x 10^9/L, haemoglobin 10.2 gm/dL and a platelet count of 310 x 10^9/L, with a white cell differential of neutrophils 36%, lymphocytes 57% and monocytes 7%.

DISCUSSION

Chronic lymphoproliferative disorder is an uncommon disorder in Asia, even though it is the commonest form of haematological malignancy in the West. Since chronic lymphocytic leukaemia is the commonest type, it is not uncommon to group all the patients with persistent lymphocytosis under this type. However, it is realised that chronic lymphoproliferative disorder is very heterogeneous and the clinical behaviour and the prognosis may be different in the subgroups. It is therefore important to identify the subtype of a patient with lymphocytosis so that optimal treatment could be given.

The common subtypes of the chronic lymphoproliferative disorders and their typical clinico-pathological features are given in Table III[13].

Three of our four patients were males, with a median age of 62 years. None of them had significant lymphadenopathy but two patients had very large spleens and one had moderate splenomegaly. The mean WBC was 15 x 1 0^9/L with the range of 9.1 to 20 x 10^9/L. Two patients had some weak positivity with tartrate-resistant acid phosphatase. The pattern of splenic involvement in case 4, who had splenectomy done, was mainly the involvement of

Table III - Features of B-chronic lymphoproliferative disorders

	Chronic lymphocytic leukaemia	Prolymphocytic leukaemia	Splenic lymphoma with villus lymphocytes	Hairy cell leukaemia	Hairy cell leukaemia variant
Male: female ratio	2:1	2:1	2:1	4:1	4:1
Palpable splenomegaly	+	++	++	++	++
Palpable lymphadenopathy	++	±	±	±	±
Mean WBC (10^9/L)	100	175	20	5	90
Tartrate-resistant acid phosphate	-	±	±	+	±
Pattern of splenic involvement	White pulp ± Red pulp	White pulp ± Red pulp	White pulp + Red pulp	Red pulp	Red pulp
Immunophenotype					
CD5	+++	±	±	-	-
CD19	++	+++	+++	+++	+++
CD20	+	+++	+++	+++	+++
CD22	±	+++	+++	+++	+++
CD11c	+	±	±	+++	±

± indicates positive in few cases
+ indicates positive in >10% of cases
++ indicates positive in >50% of cases
+++ indicates positive in >90% of cases

the white pulp with extension into the red pulp (Figs 1 & 2). The lymphocytes in all 4 cases were positive with CD19 and CD20 (Table II) confirming the B-cell origin. Three cases had some positivity with CD5 which is usually a marker of CLL[14]. CD5 positivity was found in 19% of cases of SLVL in other studies[14]. None of the cases was positive with CD 11c, making the diagnosis of hairy cell leukaemia (HCL) unlikely. Most importantly, the morphology of the lymphocytes in all 4 cases were not typical of CLL or HCL but were characteristic of SLVL. They were larger than the CLL lymphocytes, with moderate amount of cytoplasm. They had condensed nuclear chromation with small nucleolus. Some had short thin cytoplasmic villi mainly towards one pole of the cell (Fig 3).

All these disorders have overlapping clinical, laboratory and immunophenotypic features, therefore it is important to take all these features into consideration in making a diagnosis. Taking the whole picture of significant splenomegaly with no lymphadenopathy, a mean WBC count of 15 x 10^9/L and the morphology of the lymphocytes, with moderate amount of cytoplasm and fine hairy projections at one pole of the cell, these cases best fit a diagnosis of SLVL rather than any other subtype of chronic lymphoproliferative disorder. It is important to recognise this subtype since the main clinical problem encountered is due to hypersplenism, as was the case in 2 of our patients with thrombocytopaenia. Splenectomy is clearly the treatment of choice in symptomatic patients[15]. Two of our patients with huge spleens and thrombocytopaenia including case 4 with significant splenic pain, underwent splenectomy.

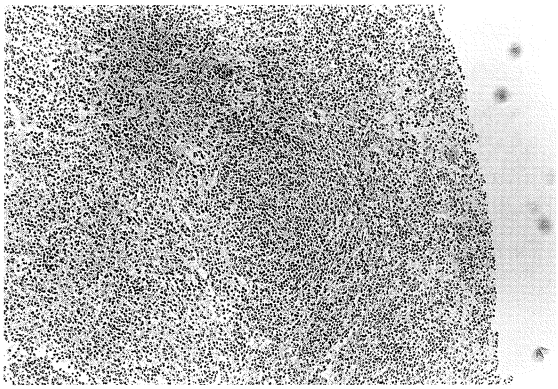

Fig 1 - Section of the spleen showing white pulp involvement with infiltration of the red pulp (H&E x 100)

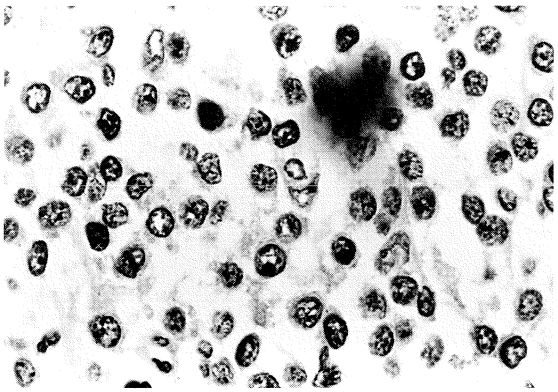

Fig 2 - White pulp infiltration at a higher magnification (H & E x 1000) showing intermediate sized lymphocytes

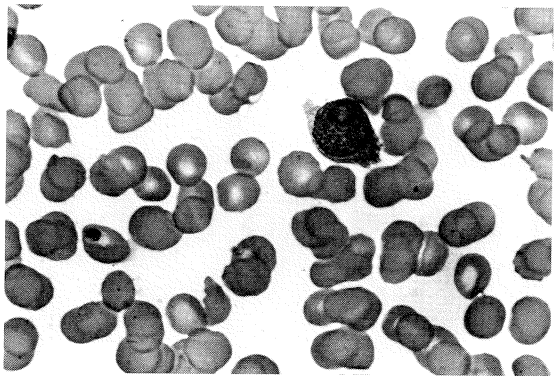

Fig 3 - Peripheral blood film showing large lymphoid cells with short irregular villi with polar concentration. It also shows a single nucleolus (MGG x 1000)

We conclude that in any patient with persistent lymphocytosis of mild to moderate degree, with splenomegaly, but with minimal or no lymphadenopathy and morphologically the lymphocytes being not typical of CLL or HCL, then SLVL should be considered as the most likely diagnosis. It is important to differentiate this disorder from the common type of chronic lymphoproliferative disorder, CLL, as the management may be different if they are symptomatic.

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