

# Autoimmunity in chronic lymphocytic leukaemia

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**Summary:** Seventy-nine patients with chronic lymphocytic leukaemia were evaluated for the presence of autoimmune diseases and autoantibodies. One patient has polymyositis and two additional patients presented with features suggestive of pernicious anaemia and chronic active hepatitis.

The Coombs' direct test was positive in 7% and immune thrombocytopenia was present in 8.1% of patients. Five (7%) patients had M-protein in the serum. No increased frequency of other autoantibodies was noted in our study group.

We conclude that the propensity to develop antibodies is restricted only to the haematopoietic system and that there is no increased frequency of non-haematological autoimmune diseases in chronic lymphatic leukaemia.

## Introduction

Patients with chronic lymphocytic leukaemia (CLL) may develop features of autoimmunity. Coombs' positive haemolytic anaemia occurs in 15% to 35% of patients at some time during the course of the disease.<sup>1</sup> Autoimmune thrombocytopenia and neutropenia have been reported as well.<sup>2,3</sup>

However, the occurrence of autoimmune diseases during the course of CLL is rare and only isolated cases have been reported hitherto.<sup>4</sup> We have evaluated, in a prospective study, whether there is an increased incidence of autoimmune diseases and autoantibodies in CLL patients.

## Materials and methods

Seventy-nine B-type CLL patients followed in the Haematology Division, Beilinson Medical Center, from January 1975 to December 1984, were included in the study. The criterion for diagnosis of CLL was a sustained and absolute lymphocytosis of  $> 10 \times 10^9$  cells/litre in the peripheral blood. Bone marrow aspiration was not done in every patient and was not a prerequisite for the diagnosis. All CLL patients evaluated were of B-type as confirmed by the presence of low intensity immunoglobulin staining on the cell surface membrane. The

cells had receptors for the Fc fragment of IgG and for complement as well as receptors for mouse erythrocytes.<sup>4</sup> Fifty-three living patients were evaluated prospectively for the presence of autoimmune diseases. Case records of another 26 patients, 13 of whom had died during the follow-up for other reasons, were reviewed retrospectively.

In each case the following information was recorded: symptoms suggestive of autoimmune disease and physical findings according to accepted criteria.<sup>5</sup> Baseline laboratory studies included the following: urinalysis, peripheral blood count, serum protein electrophoresis and immunoglobulins, direct and indirect Coombs' test, LE cells, antinuclear factor, Rose-Waaler and latex tests, VDRL, cryoglobulin, cryofibrinogen, complement: C3, C4, CH50 and free thyroxine.

Antinuclear factor was defined as positive when the titre was above 1:80. Autoimmune thrombocytopenia was indicated by (a) platelet count less than  $10 \times 10^{10}/l$ , (b) adequate or increased number of megakaryocytes in the bone marrow aspirate and/or biopsy,<sup>6</sup> (c) no splenomegaly. Assays of immunoglobulins on the platelet antibodies in the sera of the patients were not performed.

## Results

Seventy-nine patients with B-type CLL were evaluated. Thirty-seven patients were male, ranging in age from 46 to 85 years, and 42 patients were

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female, ranging in age from 50 to 77 years at presentation.

One patient with autoimmune disease was identified (Case 1). Two additional patients were identified with clinical evidence suggestive of autoimmune diseases (Cases 2 and 3).

A review of the clinical features of other patients was negative for autoimmune diseases. Laboratory features of the patients on this study group are summarized in Table I. Coombs' direct test was positive in 7% of patients. Immune thrombocytopenia was present in 8.1%, and 5 (7%) patients had a monoclonal peak on serum immunoelectrophoresis (4-IgM, 1-IgG K).

#### Case 1

A 61 year old female was admitted to the Department of Internal Medicine 'D' with a 9 month history of pain in the fingers and knees and muscle weakness of the hip and thigh muscles. She had been diagnosed 6 months previously as having CLL in view of persistent leukocytosis  $20 \times 10^9/l$  and lymphocytosis (60%) of 'B' type.

Physical examination revealed weak muscles of hips and thighs and swollen fingers and hands. There were areas of depigmentation and numerous telangiectatic lesions over the fingers.

Laboratory evaluation revealed: erythrocyte sedimentation rate 60mm/hour and creatine kinase 190IU/l (normal 100), antinuclear antibodies were detected in a titre of 1:1280.

Electromyography revealed the presence of multiple short polyphasic waves with spikes. Capillaroscopy of the fingernails showed the presence of large avascular areas and blurring of the capillary structure.

Muscle biopsy showed muscle fibre necrosis with perivascular inflammatory changes. In view of these findings, connective tissue disease with polymyositis was diagnosed and she was treated with prednisone.

#### Case 2

A 61 year old Israeli woman who had been under the care of the Haematology Department since 1984 for CLL was admitted two years later with complaints of weakness. Laboratory studies showed white cell count  $95 \times 10^9/l$  with 90% lymphocytes of B-type, platelets  $240 \times 10^9/l$ . Haemoglobin 8.5g/dl, MCV 115, reticulocytes 9%. Coombs' direct and indirect tests were negative; B12 90 ng/l, folic acid 3.8  $\mu\text{g}/l$ . Bone marrow aspiration and biopsy showed hypercellular marrow, infiltration by small lymphocytes and prominent megaloblastic changes in the erythroid series. She was treated with vitamin B12 injections with a good response.

#### Case 3

A 58 year old man was diagnosed as having CLL in 1980. He did well until February 1984 when he was admitted to hospital with hepatitis B surface antigen positive infectious hepatitis. The hepatocellular enzymes remained elevated in the next two years. Anti-mitochondrial and anti-smooth muscle antibodies, however, were not detected in the serum and the patient refused liver biopsy. Over the next two years progressive deterioration of the liver function was noted. He died of sepsis and liver failure.

## Discussion

Various autoimmune phenomena are known to complicate the course of CLL. However, the propensity to develop autoantibodies is restricted to the haematopoietic system. Interestingly, these antibodies are not produced by the malignant B-type cell clone.<sup>4</sup> The patients develop either haemolytic anaemia, thrombocytopenic purpura or neutropenia related to autoantibodies to red blood cells, platelets or neutrophils, respectively.<sup>1,3,7</sup> Rarely patients present with a syndrome resembling pure red cell aplasia. A direct effect of suppressor T-cells is thought to operate,<sup>8</sup> although in some idiopathic cases autoantibodies are implicated.<sup>9</sup>

The occurrence of autoimmune diseases during the course of CLL is rare. Isolated case reports have recorded the occurrence in CLL patients of autoimmune hyperthyroidism,<sup>10</sup> immune deposited nephritis,<sup>11</sup> and cryoglobulinaemia with cold urticaria and cryofibrinogenaemia.<sup>12</sup>

**Table I** Autoimmunity in CLL - laboratory features

	No. of patients checked	No. of pathological results
Coombs' test (direct)	72	5 (7%)
Panhypogammaglobulinaemia	71	58 (62%)
Monoclonal serum protein	71	5 (7%)
Autoimmune thrombocytopenia	79	7 (8%)
LE cells	50	none
ANF	52	1 (Case 1)
Rose-Waaler test	51	none
Latex test	51	none
VDRL	49	none
Cryoglobulin	53	none
Cryofibrinogen	53	none
C3	48	none
C4	50	none
CH50	50	none
Free thyroxine	50	none

To the best of our knowledge, prospective evaluation of the incidence of autoimmune disease in a large group of CLL patients has not been previously reported.

Seventy-nine patients with B-type CLL were included in the study group. Only one patient with definite autoimmune disease was identified. In this patient the diagnosis of connective tissue disease with polymyositis and CLL seems well established. In the second patient a diagnosis of pernicious anaemia was highly suggestive but a firm diagnosis was not reached. The third patient presented with clinical symptoms suggestive of chronic active hepatitis but a tissue diagnosis was not obtained. None of the other patients had any laboratory evidence suggestive of non-haematological autoimmune disease. The battery of blood tests that tested various immune functions did not yield any abnormal results.

The increased incidence of autoimmune haemolytic anaemia and autoimmune thrombocytopenia in CLL patients was confirmed also in our study group. Why they should develop these autoimmune

disorders, particularly in the face of diminished B-cell function, is unknown. It is possible that the autoimmune process is caused by an imbalance of the T-cell subset. Disturbances of T-cells have been reported by many authors, with reduced numbers of T-helper cells and increased numbers of T-suppressor cells<sup>13</sup> and concomitant changes in helper and suppressor function.<sup>14</sup> Abnormalities of macrophage function may be responsible for some of the immune abnormalities.<sup>4</sup> An additional interesting hypothesis is that previous therapy by irradiation or alkylating agents may trigger autoimmune complications in some of the patients.<sup>15</sup>

In conclusion, we have demonstrated in our study that the propensity to develop autoantibodies is restricted to the haematopoietic system. No increased frequency of autoimmune diseases and autoantibodies was detected. Although connective tissue disease, with polymyositis and chronic active hepatitis have not been described in CLL so far we ascribe their occurrence here to a random association.

## References

1. Bergsagel, D.E. The chronic leukemias: a review of disease manifestations and the aims of therapy. *Can Med Assoc J* 1967, **96**: 1615-1620.
2. Carey, R.W., McGinnis, A., Jacobson, B.M. & Carralho, A. Idiopathic thrombocytopenic purpura complicating chronic lymphatic leukemia. *Arch Intern Med* 1976, **136**: 62-66.
3. Rustagi, P., Zolkowski, H.T., Currie, M. & Luge, G. Antigranulocyte antibodies in chronic lymphocytic leukemia and other chronic lymphoproliferative disorders. *Blood* 1983, **62** (Suppl. 1): 106 (abstract).
4. Gale, R.P. & Foon, K.A. Chronic lymphatic leukemia. *Ann Intern Med* 1985, **103**: 101-102.
5. Gilliland, B. & Mannik, M. Immune complex disease. In: Petersdorf, R.G., Adams, R.D., Braunwald, E., Isselbacher, K.J., Martin, J.B. & Wilson, J.D. (eds) *Harrison's Principles of Internal Medicine*, 10th edition McGraw-Hill, New York, 1983, pp. 378-382.
6. Rubinstein, D.B. & Longo, D.L. Peripheral destruction of platelets in chronic lymphocytic leukemia: recognition, prognosis and therapeutic implications. *Am J Med* 1981, **71**: 729-732.
7. Ebbe, S., Wittles, B. & Dameshek, A. Autoimmune thrombocytopenic purpura (ITP type) with chronic lymphatic leukemia. *Blood* 1962, **19**: 23-27.
8. Managan, K.D., Chikkapa, G. & Farley, P.C. T-gamma (T) cells suppress growth of erythroid colony-forming units in pure red cell aplasia of B-cell chronic lymphocytic leukemia. *J Clin Invest* 1982, **70**: 1148-1156.
9. Abeloff, M.D. & Waterbury, L. Pure red cell aplasia and chronic lymphocytic leukemia. *Arch Intern Med* 1974, **134**: 721-724.
10. Hauybenstock, A. & Zalusky, R. Autoimmune hyperthyroidism and thrombocytopenia developed in a patient with chronic lymphocytic leukemia. *Am J Hematol* 1985, **19**: 281-283.
11. Gilboa, N., Durnate, D., Guggenheim, S. *et al.* Immune deposit nephritis and single component cryoglobulinemia associated with chronic lymphocytic leukemia. *Nephron* 1979, **24**: 223-231.
12. Rawnsley, H.M. & Shelley, W.B. Cold urticaria with cryoglobulinemia in a patient with chronic lymphocytic leukemia. *Arch Dermatol* 1986, **98**: 12-17.
13. Catovsky, D., Lauria, F., Matutes, E. *et al.* Increase in T lymphocytes in B cell chronic lymphocytic leukaemia. *Br J Haematol* 1981, **47**: 539-544.
14. Kay, N.E. Abnormal T cell subpopulation function in CLL: excessive suppressor T and deficient helper T activity with respect to B cell proliferation. *Blood* 1981, **57**: 418-420.
15. Lewis, R.B., Schwartz, R.S. & Demeshek, W. X-radiation and alkylating agents as possible 'trigger' mechanism in the autoimmune complications of malignant lymphoproliferative disease. *Clin Exp Immunol* 1966, **1**: 3-11.