

RAPID TRANSFORMATION OF ATYPICAL CHRONIC LYMPHOCYTIC LEUKEMIA TO ACUTE LYMPHOBLASTIC LEUKEMIA

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Amin U. Haq, Darryl M. Williams, John R. Clement, Leonard M. Bowen (Department of Medicine, Veterans Administration Medical Center and Louisiana State University, Shreveport, Louisiana.)

Abstract

Transformation of chronic lymphocytic leukemia to acute lymphoblastic leukemia is extremely rare. We describe an elderly patient whose lymphocytes on presentation were morphologically characteristic of chronic lymphocytic leukemia, but changed to lymphoblasts in a very short interval. Peripheral blood mononuclear cells were tested for surface immunoglobulins and T65 antigen at initial presentation as well as at subsequent blastic transformation; on both occasions the majority of cells were devoid of both cell markers. Blast cells in the peripheral blood were positive for terminal deoxynucleotidyl transferase, thus establishing their lymphoid origin (JPMA 37: 269,1987). Most cases of chronic lymphocytic leukemia (CLL) are characterized by circulating surface immunoglobulin positive (slg+) lymphocytes, derived from a single B cell clone. Another antigen, T65, has recently been demonstrated on the surface of nonsecretory CLL cells with the use of TiO1 monoclonal antibody. T65 antigen is a T cell specific antigen which is not present on normal B cells but is detected on the surface of nonsecretory, surface immunoglobulin-positive (slg+) cells of CLL patients, thus providing an additional marker for detection of CLL.¹ Transformation of CLL to acute lymphoblastic leukemia (ALL), though extremely rare, has been reported before^{2,8}. However, all the patients who underwent cell marker studies during the chronic and acute phases of the disease, demonstrated slg+ phenotype^{2,7}. T65 antigen was not studied in any of these patients. We describe a unique patient whose lymphocytes, morphologically, were characteristic of CLL on presentation, but lacked slg and T65 antigen (slg-Ti 01). Within 4 months acute blastic transformation supervened and shortly thereafter the patient died.

CASE REPORT

A 67 year old black man was hospitalized for biopsy of a vocal cord lesion in December 1983. Spleen was palpable 5 cm below the left costal margin, liver was not palpable, and there was no lymphadenopathy. His hemoglobin was 9.3 g/dl, and his platelets were 47 x 10⁹/L. The white blood cell (WBC) count was 118 x 10⁹/L with 87% lymphocytes. Lymphocytes were small and mature with rare (< 1%) nucleolated forms. Fifteen percent of WBC were smudge cells. Bone marrow was hypercellular with abundant megakaryocytes, a dense infiltrate of small, well differentiated lymphocytes, and 1% blast cells. T and B lymphocyte quantitation of peripheral blood mononuclear cells (PBMN) was accomplished by a T and B cell kit (HYBRITECH CA) based on an immunometric fluorescence method. T cells were identified by TiO1 monoclonal antibody which recognizes a 65,000 MW antigen (T65) on T-cell membrane, while B-cells were identified by Flit anti-human Ig (polyclonal goat Ig specific for IgG, IgA and IgM heavy chains and kappa and lambda light chains on cell membrane). T65 antigen is also present on CLL cells bearing surface Ig (I). Of the patient's PBMN, T-cells were 8.5%, B-cells were 15.2% and the rest were negative for T and B-cell markers. Cells of a healthy volunteer were analyzed concurrently and had normal values. Serum immunoglobulins were normal. The patient was considered to have CLL and was started on Chiorambucil 6 mg and prednisone

30 mg daily. At the start of chemotherapy the WBC had risen to $242 \times 10^9/L$ but fell to $17 \times 10^9/L$ after 3 weeks of treatment. The chemotherapy was intermittently administered to the patient for the next 3 months. In March 1984, while the patient was still on chiorambucil and prednisone, the WBC count had gradually risen to $250 \times 10^9/L$ with mature lymphocytes 84%, nucleolated lymphocytes with clumped chromatin 4%, neutrophils 9%, and monocytes 3%. Bone marrow was infiltrated predominantly with mature lymphocytes, but lymphocytes of varying immaturity (including blasts cells, 4%) were present. The chemotherapy was changed to cyclophosphamide, vincristine and prednisone (COP). Two weeks after initiation of COP the WBC count fell to $186 \times 10^9/L$ but there was a dramatic change in the morphology of the WBC; 92% of the cells were now nucleolated blasts. Bone marrow, likewise, was diffusely infiltrated with immature blast cells. Cytochemical staining of bone marrow cells (peroxidase, Sudan black, alpha-naphthyl acetate esterase, and naphtholAS-Dichloroacetate) was negative; however, 15-20% of blasts showed coarse granular positivity with Periodic acid-Schiff stain. There was no chromosomal abnormality in marrow cells. Terminal deoxynucleotidyl transferase (TdT) was positive in 80% of PBMN as determined by indirect fluorescence technique. PBMN were also studied for T and B cell markers and the majority of cells once again were negative for both markers (T cells 1%, B cells 7%, non T & B 92%). From these studies it was concluded that transformation to acute lymphoblastic leukemia had occurred. The patient was treated with one course of vincristine, prednisone, daunorubicin and L-asparaginase with subsequent severe leukopenia and sepsis. Bone marrow aspirate and biopsy demonstrated persistence of leukemia. The patient refused further chemotherapy and died two months later.

DISCUSSION

Several possibilities should be considered regarding the nature of the disease at initial presentation: (a) the patient may have had an abnormal form of CLL derived from a primitive B cell clone; (b) the initial disease may have been prolymphocytic or "prolymphocytoid" leukemia; (c) the patient had ALL masquerading as CLL. The following evidence suggests that the patient initially had CLL: (a) lymphocytes were small with scanty cytoplasm and well condensed nuclear chromatin; (b) nucleolated cells were rare; (c) smudge cells were abundant; (d) response to chiorambucil and prednisone was dramatic and lasted for approximately 3 months. Absence of surface immunoglobulin (sIg) and T65 antigen (TiO1) as was determined in this patient, does not exclude the diagnosis of CLL. Royston et al studied 15 patients of CLL with both markers and found 4 which were sIg- and T101-, all other were sIg+ T101+ phenotype⁷. There is general agreement that CLL cells represent immature B cells, arrested at an early stage of lymphocyte differentiation. Surface immunoglobulins are detected in a later stage of B cell differentiation the earlier stages may only show heavy and light chain immunoglobulin genes rearrangement or intracytoplasmic Ig expression⁹. Presence of T65 antigen on immature CLL cells and absence on mature B cells of normal or abnormal origin has led to the hypothesis that this antigen is a marker of immature B cells. However, the relationship of T65 antigen to various stages of B cell differentiation is unknown. It is possible that earlier stages of B cell differentiation, prior to acquisition of sIg, lack T65 antigen. It is noteworthy that 4 patients of CLL described by Royston et al which were sIg-, were also TiO1-, supporting this contention.

There were also several features suggestive of prolymphocytic leukemia.¹⁰ The WBC count was high, spleen was enlarged and there were no palpable lymph nodes. Moreover, the sex and age of the patient and the aggressive nature of disease were also in favour of prolymphocytic leukemia. However, this consideration is unlikely because nucleolated cells were rare in our patient, while nucleolated prolymphocytes are the predominant cells in prolymphocytic leukemia. Furthermore, unlike the lymphocytes of this patient which lacked sIg, the prolymphocytes are characterized by dense surface immunoglobulins.¹¹ "Prolymphocytoid" transformation of CLL is characterized by gradual appearance

of immature cells in peripheral blood indistinguishable from proly. mlymphocytes, ultimately resulting in two populations of cells; mature well differentiated lymphocytes and immature prolymphocytes. However, all 15 patients of prolymphocytoid transformation reported in two studies^{12,13} had slg+ prolymphocytes. In one study density of sig was greater on prolymphocytes than on small lymphocytes¹³ while in the other study it was the exact opposite; the density of slg was greater on small lymphocytes than on prolymphocytes.¹²

Another possibility, though less likely, exists that the patient initially had ALL masquerading as CLL. TdT is uniformly negative in CLL. Documentation of TdT at presentation might have clarified this consideration.

Although the nature of the disease at initial presentation may be a matter of debate, there is little doubt regarding the final transformation to ALL. This was documented by peripheral blood and bone marrow morphology, negative peroxidase and positive PAS stains and positive TdT activity in 80% of the cells. Based on available evidence, we favour the possibility that the patient at presentation had a more primitive type of CLL than common CLL, which transformed to ALL, either directly or through an intermediate stage of prolymphocytoid leukemia.

Transformation of CLL to ALL is very uncommon; only sixteen cases have been reported.

Transformation may be chemotherapy related, or it may occur spontaneously. A survey of literature identified 6 cases^{2,4,8} in which CLL transformed to ALL within one year; detailed immune studies were performed in three^{2,4}, and the results indicated that the chronic and acute phase cells had identical heavy and light chain immunoglobulins in all cases. Blastic transformation in our patient occurred in a very short interval. It is unlikely that this transformation resulted from the limited amount of concentrated chemotherapy. Thus, this case and the cases mentioned above strongly suggest that in a small number of CLL patients transformation to ALL occurs as part of the natural history of the disease.

REFERENCES

1. Royston, I., Majda, J.A., Baird, S.M., Meserve, B.L. and Griffiths, J.C. Human T cell antigens defined by monoclonal antibodies. The 65,000 dalton antigen of T cells (T65) is also found on chronic lymphocytic leukemia cells bearing surface immunoglobulin. *J. Immunol.*, 1980; 125:725.
2. Brouet, J.C., Preud'homme, J.L., Seligmann, M. and Bernard, M. Blast cells with monoclonal surface immunoglobulin in two cases of acute blast crisis supervening on chronic lymphocytic leukaemia. *Br.Med. J.*, 1973;4:23.
3. Frenkel, E.P., Ligler, F.S., Graham, M.S., Hernandez, LA., Kettman, J.R. Jr., and Smith, R.G. Acute lymphocytic leukemia transformation of chronic lymphocytic leukemia; substantiation by flow cytometry. *Am. J. Hematol.*, 1981; 10:391.
4. Januszewicz, E., Cooper, LA., Pilkington, G. and Jose, D. Blastic transformation of chronic lymphocytic leukemia. *Am. J. Hematol.*, 1983; 15 :299.
5. Eridani, S., Parry, H., Glass, U. and Greaves, M. Acute lymphoblastic leukemia supervening in a case of chronic lymphocytic leukemia after continuous 3-year treatment with chlorambucil. *Cancer*, 1984; 54 :397.
6. Laurent, G., Gourdin, M.F., Flandrin, G., Kuhlein, E., Pris, J. and Reyes, F. Acute blast crisis in a patient with chronic lymphocytic leukemia. Immunoperoxidase study. *Acta Haematol.*, 1981;65:60.
7. Jacobs, A.D., Schroff, R.W. and Gale, R.P. Acute transformation of chronic lymphocytic leukemia. *Med. Pediatr. Oncol.*, 1984; 12:318.
8. ZaArabi, M.H., Grunwald, H.W. and Rosner, F. Chronic lymphocytic leukemia terminating in acute leukemia. *Arch. Intern. Med.*, 1977; 137:1059.
9. Foa, R., Migone, N., Saitta, M., Fierro, M.T., Giubellino, M.C., Luso, P., Cordero, di Montezemolo,

- L., Miniero, R. and Lauaria, F. Different stages of B cell differentiation in nonT acute lymphoblastic leukemia. *J. Clin. Invest.*, 1984; 74: 1756.
10. Galton, D.A.G., Goldman, L.M., Wiltshaw, E., Catovsky, D., Henry, K. and Goldenberg, G.J. Prolymphocytic leukaemia. *Br. J. Haematol.*, 1974; 27 : 7.
11. Catovsky, D., Cherchi, M., Gaiton, D.A.G., Hoffbrand, A.V. and Ganeshaguru, K. Cell differentiation in B- and T4ymphoproliferative disorders, in differentiation of normal and neoplastic hematopoietic cells. *Cold Spring Harbor Conference on Cell Proliferation*. Edited by Clarkson, B. et al. New York, Cold Spring Harbor, 1978; 5:811.
12. Enno, A., Catovsky, D., O'Brien, M., Cherchi, M., Kumaran, T.O. and Galton, D.A.G. "Prolymphocytoid" transformation of chronic lymphocytic leukaemia. *Br. J. Haematol.*, 1979; 41: 9.
13. Kjeldsberg, C.R. and Marty, J. Prolymphocytic transformation of chronic lymphocytic leukemia. *Cancer*, 1981; 48:2447.