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The Erythropoiesis in Acute Lymphoblastic Leukaemia A Morphologic Study

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Summary

The erythropoietic part of the bone marrow has been morphologically analyzed in 18 patients with acute lymphoblastic leukaemia, 44 patients with acute myeloblastic leukaemia and in 20 controls. There were significant differences between the findings in the lymphoid and the myeloid leukaemias and it seems possible that the erythropoietic cells are not involved in the leukaemic process in the lymphoblastic leukaemias in contradiction to the myeloid ones.

Introduction

The morphologic identification of the pluripotent stem cell has always been controversial but it is possible that this cell at least looks like a small lymphocyte (for review see *Rosse* (1) and *Izak* (2)). The findings of the Philadelphia-chromosome in some cases of acute lymphoblastic leukaemia (ALL) in both adults (3, 4) and in children (5) suggest that this chromosome aberration can occur in a pluripotent stem cell which can proliferate along both a lymphoid cell line and a myeloid cell line. Studies of the enzyme terminal deoxynucleotidyl transferase have revealed the lymphoid nature of the blastic cells in some cases of advanced chronic myeloid leukaemia (CML) (6, 7) and polycythemia vera (8). A lymphoid blastic crisis has also been reported at the onset of CML (9). All these findings are compatible with a close relationship between the lymphoblasts and the myeloid and erythroid compartments of the bone marrow.

In 1971 *Krogh Jensen* and *Killmann* (10) stressed the importance of chromosome studies in ALL to find out if the abnormalities were restricted to the leukaemic lymphoblasts or could be found in differentiating haemopoietic precursor cells too. Earlier morphologic studies of the erythropoiesis in myeloid leukaemias (11) have shown elevated mitotic indices (MI) concomitant with a 'shift to the left' as signs of 'leukaemicness' of the erythroid cells. The aim of the present work was to investigate if there were any signs of leukaemic involvement of the erythroblasts in ALL.

Material and Methods

May-Grünwald-Giemsa stained bone marrow smears from 62 patients with acute leukaemias were investigated at the time of diagnosis. At least 500 erythroblasts were then examined in each patient and classified according to *Sjögren* (11). Proerythroblasts and basophilic erythroblasts were pooled into one group and denominated basophilic erythroblasts. The proportion of erythroblasts with a megaloblastic morphology was determined. A mitotic index of all the erythroblasts including the orthochromatic ones was also calculated. At least 18 mitoses were counted in each patient. A cell was considered to be in mitosis from the stage of partial loss of nuclear membrane in prophase until nuclear reconstitution had appeared at the end of the telophase. All the differential countings and mitotic countings were made by the author.

Patients and controls

Pertinent haematologic data are given in Table 1. The AML patients and the normals have been described earlier (11).

Statistics

Nonparametric statistics were used. The results are given as interquartile range (Q_1–Q_3). The

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Table 1 Haematologic data of 62 patients with acute leukaemias at the time of diagnosis and those of 20 normals

Group	M/F	Age, years (range)	Hb, g/l (Q_1–Q_3)	WBC x 10^{-9}/l (Q_1–Q_3)
ALL	11/7	1.7–35	65– 93	4.2–38.3
AML	18/26	10 –88	65–106	3.2–35.0
Normals	9/11	19 –82	131–144	4.2– 7.0

Q_1–Q_3 = interquartile range.

Mann-Whitney two-tailed U-test and the Spearman two-tailed rank correlation test were used to assert significance of the results.

Results

The MI of the ALL patients were significantly lower than those of the AML patients ($p < 0.005$). There was no difference between the ALL patients and the normals (Table 2).

The MI of the ALL patients were significantly increasing with raising proportions of basophilic erythroblasts among the erythroid precursor cells ($r_S = 0.84$, $p < 0.001$).

There was no significant 'shift to the left' within the erythropoietic pool of the ALL patients (Table 2).

There were significantly more megaloblasts in the leukaemia groups compared to the normals ($p < 0.001$) (Table 2). There was no significant relation between the proportion of megaloblasts and the MI.

Discussion

The rapid development of anaemia is a characteristic clinical feature of both the acute myeloblastic (AML) and the acute lymphoblastic (ALL) leukaemias. Mostly the proportion of erythroblasts in the bone marrow is quite low and the erythropoietic precursors often present with megaloblastoid changes and other signs of a disturbed differentiation. In this study slight megaloblastic changes of the erythroblasts were found in both the ALL and the AML cases. A megaloblastic maturation indicating a disturbed DNA synthesis has been reported in a great variety of haematologic neoplasms (11, 12) and may result from various causes, e.g. parasitization of folate and/or vitamin B_{12} by neoplastic tissue or leukaemic involvement of the erythropoiesis. Megaloblastoid changes seem to be rather unspecific signs of a defective differentiation and may thus occur without influencing the karyotype (13).

In the present investigation the ALL patients showed normal MI concomitant with normal frequencies of early precursors within the erythropoiesis. This is in contradiction to the findings in nearly all types of the myeloid leukaemias where a series of cytokinetic and morphologic studies have indicated a maturation arrest of the early polychromatic erytroblasts resulting in an abnormally large proportion of basophilic erythroblasts and elevated MI (for review see *Sjögren* (11)). This pure morphologic study of the erythropoiesis in

Table 2 Frequencies of basophilic erythroblasts, megaloblasts and mitoses in bone marrow from 62 patients with acute leukaemias and from 20 normals

Group	n	Basophilic erythroblasts	Megaloblasts	Mitoses
ALL	18	25–36 ns	4.2– 7.8 a)	2.4–3.3 ns
AML	44	32–41 a)	3.5–13 a)	3.0–4.5 c)
Normals	20	30–33	1.1– 2.4	2.8–3.4

Figures give interquartile range of percentages of all erythroblasts and significance of difference between patients and normals: a) $p < 0.001$, c) $0.01 < p < 0.05$, ns = $p > 0.05$.

ALL does not support the idea of a leukaemic involvement of the erythroid cell line. Thus a crowding out of the erythropoietic precursor cells by the malignant lymphoblasts would probably be the main reason for the development of anaemia in ALL. Other mechanisms, e.g. a significant suppression of the erythropoiesis by malignant T-lymphocytes (14) or haemolysis due to autoantibodies and/or an enlarged spleen may of course contribute to the anaemia. The ALL in children and younger adults could probably arise in one single cell line viz. the lymphoid one.

References

1 *Rosse, C.:* Precursor cells to erythroblasts and to small lymphocytes of the bone marrow. In G.E. Wolstenholme, M. O'Connor (eds) Haemopoietic Stem Cells, pp 105–29. Associated Scientific Publishers, Amsterdam

2 *Izak, G.:* Erythroid cell differentiation and maturation. In E.B. Brown (ed) Progress in Hematology, vol X, pp 1–41. Grune & Stratton, New York

3 *Bloomfield, C.D., L.C. Peterson, J.J. Yunis, R.D. Brunning:* The Philadelphia chromosome (Ph^1) in adults presenting with acute leukaemia: A comparison of Ph^1+ and Ph^1– patients. Br. J. Haematol. 36 (1977) 347–358

4 *Gibbs, T.J., M.V. Wheeler, A.J. Bellingham, S. Walker:* The significance of the Philadelphia chromosome in acute lymphoblastic leukaemia: A report of two cases. Br. J. Haematol. 37 (1977) 447–453

5 *Rausen, A.R., H.J. Kim, Y. Burstein, S. Rand, R. M. McCaffrey, P.C. Kung:* Philadelphia chromosome in acute lymphatic leukaemia of childhood Lancet 1977/II, 432

6 *Hutton, J.J., M.S. Coleman:* Terminal deoxynucleotidyl transferase measurements in the differential diagnosis of adult leukaemias. Br. J. Haematol. 34 (1976) 447–456

7 *Janossy, G., R.K. Woodruff, A. Paxton, M.F. Greaves, D. Capellaro, B. Kirk, E.M. Innes, O.B. Eden, C. Lewis, D. Catovsky, A.V. Hoffbrand:* Membrane marker and cell separation studies in Ph^1-positive leukemia. Blood 51 (1978) 861–877

8 *Hoffman, R., S. Estren, S. Kopel, S.M. Marks, R.P. McCaffrey:* Lymphoblastic-like leukemic transformation of polycythemia vera. Ann. Intern. Med. 89 (1978) 71

9 *Mauri, C., U. Torelli, U. di Prisco, V. Silingardi, T. Artusi, G. Emilia:* Lymphoid blastic crisis at the onset of chronic granulocytic leukemia. Cancer 40 (1977) 865–870

10 *Krogh Jensen, M., S.-Aa. Killmann:* Additional evidence for chromosome abnormalities in the erythroid precursors in acute leukaemia. Acta Med. Scand. 189 (1971) 97–100

11 *Sjögren, U.:* Morphologic studies of the erythropoietic part of the bone marrow in myeloid leukaemias. Scand. J. Haematol. 22 (1979) 61–66

12 *Bart, J.B.:* Megaloblastosis in hematologic malignancy. South. M. J. 66 (1973) 981–983

13 *Brandt, L., F. Mitelman, U. Sjögren:* Megaloblastic changes and chromosome abnormalities of erythropoietic cells in acute myeloid leukaemia. Acta Haematol. (Basel) 54 (1975) 280–283

14 *Hoffman, R., S. Kopel, S.D. Hsu, N. Dainiak, E.D. Zanjani:* T cell chronic lymphocytic leukemia: Presence in bone marrow and peripheral blood of cells that suppress erythropoiesis in vitro. Blood 52 (1978) 255–260

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