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Autonomous Erythropoiesis during Erythroblastic Crisis of Chronic Myelocytic Leukemia

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ABSTRACT Two patients with chronic myelocytic leukemia who developed an erythroblastic rather than a myeloblastic phase were studied with respect to whether or not the megaloblastic erythropoiesis was subject to normal control mechanisms. After transfusion, no significant reduction was observed in the percentage of nucleated erythroid precursors or of proerythroblasts in marrow or in blood reticulocytes. In one of the two patients, ferrokinetics and urinary erythropoietin levels were studied and were also compatible with the conclusion that erythropoiesis was autonomous in this rare syndrome. Three patients with clinical pictures compatible with Di Guglielmo's syndrome were studied as controls. As has been reported previously, erythropoiesis in this syndrome appeared to be responsive to normal control mechanisms. These data suggest that these two clinically similar syndromes, erythroblastic crisis of chronic myelocytic leukemia and Di Guglielmo's syndrome may represent qualitatively different defects in hematopoietic stem cells.

INTRODUCTION

Erythropoietin is considered to be responsible for control of production of erythrocytes in normal man (1). Human erythropoiesis, apparently autonomous as respects erythropoietin, has been documented in polycythemia vera in which increased erythropoiesis is observed in the absence of measurable levels, or at least at subnormal

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levels, of erythropoietin (1, 2). However, in Di Guglielmo's syndrome, the acute leukemia like illness involving erythroid precursors as well as granulocytic precursors, erythropoiesis appears responsive to normal control mechanisms. Correction of anemia by transfusion has resulted in suppression of erythropoiesis (3-7) and erythropoietin levels (4, 5). Erythropoietic and erythropoietin suppression by transfusion has been documented in a few patients with "typical" chronic myelocytic leukemia and in idiopathic myelofibrosis with myeloid metaplasia (8).

The usual terminal event in chronic myelocytic leukemia (CML)¹ is development of a myeloblastic phase characterized by gradual increase in immaturity of the granulocytic series of cells and by anemia, thrombocytopenia, consequent infection, hemorrhage, and death. On rare occasions, the "blastic phase" is characterized by erythroblastosis rather than by myeloblastosis (3, 9).

We have observed two patients in whom an erythroblastic phase developed after a fairly typical picture of CML. The difference between the responsiveness of erythropoiesis to levels of circulating red blood cells in these two patients with erythroblastic crisis of CML, as compared to three patients with Di Guglielmo's syndrome constitute the basis for this report.

METHODS

Case Reports: L. S. A 63-year old woman was found to have CML in January 1970. Sternal tenderness, spleno-

¹ *Abbreviations used in this paper:* CML, chronic myelocytic leukemia; MCV, mean corpuscular volume; PIT, plasma iron turnover.

megaly, a hemoglobin of 8 g/100 ml, white blood cells (WBC) 35,000/mm³ with neutrophilia, eosinophilia, basophilia, and a platelet count of 500,000/mm³ were present. She was treated with busulfan 6 mg/day until November 1970.

We saw her for the first time 2 mo after busulfan had been discontinued. The spleen was palpable 1 cm below the left costal margin, the hematocrit was 27% mean corpuscular volume (MCV) 115 μm³, WBC 4,200/mm³ with 40% polys, 10% bands, 20% metamyelocytes, 6% promyelocytes, 3% eosinophils, and platelets were 38,000/mm³. Leukocyte alkaline phosphatase score was 340. A Ph¹ chromosome was found in 20/20 metaphases on direct culture of marrow. Serum folate was 5.8 ng/100 ml, serum B₁₂ was 900 pg/100 ml and a Schilling test was normal. Bone marrow biopsy was hypercellular with marked erythroid hyperplasia. Marked megaloblastic changes with numerous multinucleated pronormoblasts and giant megaloblasts were seen in smears of marrow aspirate, and the M:E ratio was 1:3.

Since the time of study (Table I), she has required transfusions, but otherwise remains in a stable hematologic and clinical condition. Her marrow remains markedly megaloblastic.

B. H. A 28-yr old woman, was found to have CML in April 1968. Her disease was controlled by intermittent busulfan until February 1970. We first examined her in October 1969, at which time she had sternal tenderness and a palpable spleen. Her hematocrit was 35%, WBC 45,000/mm³ with 29% polys, 17% metamyelocytes, 12% myelocytes, 1% myeloblasts, 10% eosinophils, and 15% basophils. The red blood cells were normochromic and normocytic and the MCV was 89. The platelet count was 1.2 million/mm³. Bone marrow aspirate was cellular with granulocytic predominance and normoblast maturation was normal at that time. Cytogenetic studies revealed a typical Ph¹ chromosome in 19 of 20 metaphases and a duplicate Ph¹ chromosome in 1/20.

In February 1970 she developed fever, weakness and a nonproductive cough. She had had no chemotherapy in the preceding 2 mo. Her temperature was 40°C and the spleen was 5 cm below the left costal margin. The WBC was

37,000/mm³ with 40% polys, 10% myelocytes, 4% promyelocytes, and 4% myeloblasts. Platelets were 260,000/mm³. Her hematocrit was 30%, MCV was 110 μm³, and there were 10 nucleated red cells per 100 white blood cells. Serum folate was 5.3 ng/100 ml and B₁₂ was greater than 2,000 pg/100 ml. Bone marrow aspirate revealed megaloblastic changes in the erythroid series with multinucleated megaloblasts and bizarre nuclear fragmentation. There were also 23% myeloblasts and promyelocytes.

Following completion of the studies shown in Table I, she was treated with a combination of cytosine arabinoside and 6-mercaptopurine, with a return to a picture of CML. During this remission, the red cell morphology was normochromic normocytic with normal marrow erythroid maturation.

In early February 1971, she again entered blastic crisis. The hematocrit was 32%, WBC 88,000/mm³ with 41% myeloblasts and promyelocytes; macrocytic red cells and the marrow aspirate revealed megaloblastic and increased myeloblasts. Despite cytosine arabinoside, 6 mercaptopurine and daunomycin, she deteriorated rapidly and died April 4, 1971.

G. B. A 55-yr old man, was known to have been anemic for 2 yr at the time of study. Physical examination was normal except for pallor and a palpable spleen tip. Hematocrit was 21%, MCV was 117 μm³ and WBC was 2,000/mm³ with 38% polys, 52% lymphocytes, and 20% monocytes. Bone marrow aspirate and biopsy showed marked hypercellularity with megaloblastic erythroid hyperplasia and a shift to the left in the granulocyte series. There was aneuploidy, but no Ph¹ chromosome. After the studies shown in Table I, he subsequently developed frank acute myeloblastic leukemia and has shown a partial response to cytosine arabinoside.

E. H. A 72-yr old woman who has had anemia since 1965, was unresponsive to trials of folic acid, vitamin B₁₂ pyridoxine and androgens. At the time of her study, her hematocrit was 16%, platelets were 70,000/mm³ and WBC was 6,500/mm³ with a normal differential. The MCV was 95 μm³, and B₁₂ and folate levels were within normal limits. The bone marrow was hypercellular with marked erythroid hyper-

TABLE I
Erythropoiesis Before and After Transfusion

Patients	Hematocrit	Reticulocytes	Nucleated	Proerythro-	Serum iron	Plasma iron
			erythroid	blasts	(mg/100 ml plasma)/	
	%	per mm ³	cells in	in marrow	T _{1/2} plasma iron	turnover
			marrow		disappearance (min)	(mg/100 ml)
			%	%		whole blood
						per day
Erythroblastic crisis of CML						
L. S., pre	27	138,000	74	37	87/37	1.73
post	47	118,000	67	33	203/90	1.30
B. H., pre	34	72,000	37	18		
post	46	147,000	33	26		
Di Guglielmo's syndrome						
G. B., pre	21	63,000	68	6	36/17	1.70
post	48	38,000	39	9	145/154	0.60
E. H., pre	24	144,000	27	5	95/138	1.82
post	46	37,000	14	1	180/291	0.72
R. C., pre	24	36,000	33	7	120/117	0.69
post	45	18,000	1	1	116/94	0.37

plasia, abnormal megaloblastic erythropoiesis, and an increase in iron stores. She remains in a stable condition, requiring frequent transfusions.

R. C. A 71-yr old man was admitted to study after a 6 mo history of anorexia, fatigue, and dyspnea and anemia unresponsive to B₁₂ or folic acid. His hematocrit was 21%, MCV was 112 μm^3 , WBC was 5,700/mm³ with 45% polys, 14% bands, 35% lymphocytes, and 1 myeloblast, and platelets were 144,000/mm³. Bone marrow aspirate showed marked megaloblastosis and a shift to the left in the granulocyte series. His course subsequent to studies shown in Table I, has been that of a smoldering myeloblastic leukemia requiring only transfusion.

Hematological evaluation. By routine methods it utilized electronic counting (Coulter Electronics Inc., Model S, Hialeah, Fla.) Wright's-stained blood and marrow smears, and Giemsa and hematoxylin-eosin-stained sections of marrow biopsy. The percentage of various marrow cells was determined from differential counts of 500-1,000 cells in Wright's-stained smears of marrow aspirate. Reticulocyte percentage was based on differential counts of 1,000 erythrocytes and converted to absolute values by multiplying the percentage of reticulocytes by the red blood cell count. Ferrokinetics were determined as reviewed by Finch et al. (10). Urinary erythropoietin was assayed utilizing the method of Alexanian (11). Erythropoietin activity in concentrates from 24 h urine was assayed by injection into hypertransfused CBA female mice. This activity was compared to a curve of response to 0.2-1.0 U of National Institutes of Health Erythropoietin Standard and expressed as IU/24 h.

Transfusion regimen. All patients were studied before and after the hematocrit was raised to normal or supernormal levels by transfusion of packed red blood cells. Informed consent was obtained from the five patients before studies were initiated. Patient B. H. refused certain studies. Transfusions were given over a period of 3-4 days and studies were done 8-10 days after the start of transfusions.

RESULTS

Values for hematocrit, reticulocytes, nucleated erythroid precursors in marrow, serum iron, $t_{1/2}$ of injected radio-iron and plasma iron turnover (PIT) before and after transfusion are shown in Table I.

In the first patient with erythroblastic crisis of CML, pretransfusion reticulocytes were slightly increased (upper limit of normal in our laboratory is approximately 100,000/mm³) and the PIT was more than twice normal values (10). The fast $t_{1/2}$ of injected iron and a normal serum iron level suggest that the increased PIT reflected an increased rate of erythropoiesis (10). The discrepancy between the degree of increase in reticulocytes and PIT suggests a significant degree of ineffective erythropoiesis and this was further documented by studying iron incorporation into red cells. Only 18% of injected iron appeared in circulating red cells during 2 wk after iron injection, as compared to a normal value of 80% (10). Ineffective erythropoiesis was also evident in patient E. H. with DiGuglielmo's syndrome in whom red cell utilization of iron did not exceed 45%.

There was little evidence for significant suppression of erythropoiesis by transfusion in either patient with erythroblastic crisis of CML. In L. S., there was a slight reduction in reticulocytes, total percentage of nucleated erythrocytes in marrow and in PIT, but all values remained abnormally high. In B. H. reticulocytes and the percentage of proerythroblasts in marrow (but not total nucleated erythrocytes) increased after transfusion.

Urinary erythropoietin values were studied in L. S. and were appropriate as regards anemia or the lack thereof (1). Base-line excretion before transfusion averaged 12.2 IU/day, while after transfusion erythropoietin was < 1 IU/day.

In contrast to the two patients with erythroblastic crisis of CML, all three patients with Di Guglielmo's syndrome evidenced suppressed erythropoiesis after transfusion as judged by reticulocytes, percentage of nucleated erythrocytes in marrow, and PIT.

DISCUSSION

Correction of anemia led to markedly decreased erythropoiesis in the patients with Di Guglielmo's syndrome, as it did in at least seven other patients studied to date (3-7). Thus, it would appear that the ineffective, megaloblastic erythropoiesis which characterizes this variant of acute myeloblastic leukemia (12) is subject to normal control mechanisms.

Erythroblastic crisis is a rare terminal event in CML and presents a picture morphologically similar to Di Guglielmo's syndrome (8), and indeed has been considered as being one form of the syndrome (3). Erythropoiesis was not suppressed significantly by correction of anemia in the two patients with erythroblastic crisis of CML. Thus, it would appear that erythropoiesis in these patients is autonomous as respects normal control mechanisms, as is erythropoiesis in polycythemia vera (1, 2).

Cytogenetic studies (13) as well as studies of isoenzymes (14) suggest that CML is a clonal disease of pluripotent hematopoietic stem cells. Blastic transformation of CML may represent the emergence of a clone of more severely defective stem cells (13, 15, 16). There is cytogenetic evidence to suggest that the defect in myeloblastic leukemia can be placed at the same pluripotential cellular level (13). The pluripotential hematopoietic stem cell has been well characterized in the mouse. Erythrocytes, neutrophils, eosinophils, monocytes, and platelets are derived from this stem cell although in the normal state these compartments may be maintained by more differentiated stem cells, progeny of the pluripotential stem cell (17).

The nature of the stem cell defect which may lead to leukemia is unknown. However, the defect must confer a growth advantage since leukemic stem cells grow in preference to normal stem cells even though the latter

can be shown to persist in CML (18). This growth advantage could represent autonomous growth or excessive responsiveness to humoral growth stimuli. In either case the excessive cell numbers could induce feedback repression of normal stem cells. Erythropoietin is the only well characterized humoral hematopoietic regulating factor in man and as a consequence, current studies of autonomy of neoplastic stem cells are limited to erythroid progeny. The clinical and morphologic features of erythroblastic crisis of CML and Di Guglielmo's syndrome are virtually identical. Yet, assuming that the abnormal erythroid cells are part of the leukemic process, the former appears to be autonomous as respects erythropoietin while the latter is erythropoietin dependent. These observations suggest that the nature of the stem cell defect differs in diseases of great clinical similarity.

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