

Acta Medica Okayama

Volume 28, Issue 3

1974

Article 4

JUNE 1974

Clinical studies on iron metabolism of erythroblasts in preleukemic stage

Ikuro Kimura*

Isao Takahashi[†]

Motoharu Sugiyama[‡]

*Okayama University,

[†]Okayama University,

[‡]Okayama University,

Clinical studies on iron metabolism of erythroblasts in preleukemic stage*

Ikuro Kimura, Isao Takahashi, and Motoharu Sugiyama

Abstract

The appearance of sideroblasts in hypoplastic anemia (HA) and acute myelocytic leukemia (AML), together with their sideroblastograms, was studied. Hematological studies on cases with type III sideroblast dominance by sideroblastograms produced the following results. Type III sideroblast dominant HA was observed in three of 63 cases. Two of the above three cases had what we call "atypical factor", while the remaining one became AML in its clinical course and could be considered to be leukemia in a hypoplastic preleukemic stage. Type III sideroblast dominant AML was noted in five of 32 cases. Three of these five cases are compatible with low percentage leukemia, and one of the above three cases showed ringed sideroblasts exhibiting erythroleukemia in the terminal stage. In HA and AML, type III sideroblast dominant cases have to be examined in relation to atypical HA and atypical leukemia. Changes of iron metabolism in erythroblasts with preleukemic stage will be attributable to disturbance of erythropoiesis such as erythroid hyperplasia in bone marrow and also, in part, to disturbance of hemoglobin synthesis.

*PMID: 4280229 [PubMed - indexed for MEDLINE] Copyright ©OKAYAMA UNIVERSITY MEDICAL SCHOOL

Acta Med. Okayama 28, 173—180 (1974)

CLINICAL STUDIES ON IRON METABOLISM OF ERYTHROBLASTS IN PRELEUKEMIC STAGE

Ikuro KIMURA, Isao TAKAHASHI and Motoharu SUGIYAMA

*Department of Internal Medicine, Okayama University Medical School,
Okayama, Japan (Director: Prof. K. Hiraki)*

Received for publication, August 6, 1973

Abstract: The appearance of sideroblasts in hypoplastic anemia (HA) and acute myelocytic leukemia (AML), together with their sideroblastograms, was studied. Hematological studies on cases with type III sideroblast dominance by sideroblastograms produced the following results. Type III sideroblast dominant HA was observed in three of 63 cases. Two of the above three cases had what we call "atypical factor", while the remaining one became AML in its clinical course and could be considered to be leukemia in a hypoplastic preleukemic stage. Type III sideroblast dominant AML was noted in five of 32 cases. Three of these five cases are compatible with low percentage leukemia, and one of the above three cases showed ringed sideroblasts exhibiting erythroleukemia in the terminal stage. In HA and AML, type III sideroblast dominant cases have to be examined in relation to atypical HA and atypical leukemia. Changes of iron metabolism in erythroblasts with preleukemic stage will be attributable to disturbance of erythropoiesis such as erythroid hyperplasia in bone marrow and also, in part, to disturbance of hemoglobin synthesis.

Close clinical examination of cases with apparent hypoplastic anemia (HA) has often proved to be paroxysmal nocturnal hemoglobinuria (PNH) (1) or, in the clinical course, to be leukemia. We have already reported several cases each of the above types (2). On the other hand, in our daily clinical practice it is sometimes found (3), though rarely, that in the category of leukemia, there are cases wherein differential diagnosis is required between atypical leukemia, hypoplastic leukemia and low percentage leukemia with the bone marrow showing remarkable hypoplasia and with the blast count so low as similar to that observed in HA.

The clinical picture of HA is characterized by peripheral pancytopenia and hematopoietic disturbance in bone marrow. Its diagnosis seems to be rather easy based on hematological findings, tissue culture on the bone marrow, the sideroblastogram, and serum Fe and Cu levels. As mentioned, however, HA occasionally turns out to be PNH or leukemia. Thus, the possibility cannot be ruled out that one often includes some other diseases in so-called HA.

From hematological findings, we have already instituted atypical HA. If HA should include other diseases, it is necessary to watch for atypical HA and to study it not only in terms of peripheral blood, myelograms and serum Fe and Cu levels but also from various other aspects, so as to identify more atypical factors than those currently known.

From the above point of view, we have studied the incidence of sideroblasts and the sideroblastogram in HA, and have also carried out similar studies on acute myelocytic leukemia (AML).

MATERIALS AND METHODS

1) *Subjects :*

Involved in our present studies were 63 cases of idiopathic HA and 32 cases of AML who were admitted to our department during the period from 1952 to 1972 and were examined for sideroblasts. None of these cases had been treated previously. The cases whose clinical picture and examinations indicated evident complication by infections or hepato-renal damage were excluded from the studies. Thirty-eight normal subjects were employed as a control group.

2) *Methods :*

The method employed for sideroblasts was almost the same as that described by KAPLAN (4). The classification of sideroblasts and the preparation of the sideroblastogram were made according to our methods (5) (Fig. 1). Our studies emphasized the appearance of sideroblasts and the sideroblastogram in the subjects; in particular, the cases dominated by the type III sideroblast were statistically extracted and their hematological features were examined.

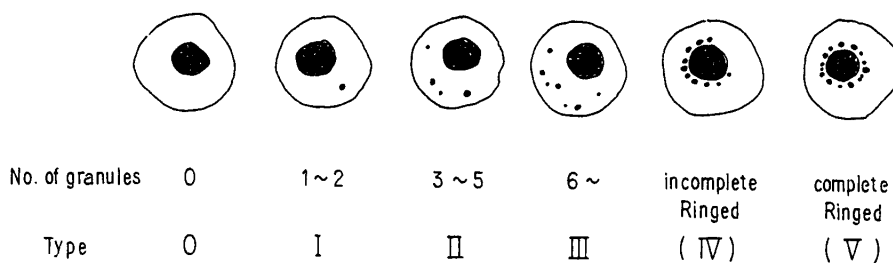


Fig. 1. Classification of sideroblast (KIMURA 1955)

RESULTS

1) *Sideroblast appearance in HA and AML :*

The appearance of sideroblasts in HA and AML is presented in the figure ; $30.6 \pm 8.2\%$ in the control group, $85.3 \pm 11.0\%$ in HA, and $67.8 \pm 24.7\%$ in AML, indicating a high incidence in HA and AML. Especially in HA statistics showed a low variance, which appeared to be characteristic. The

appearance of sideroblasts in monocytic leukemia (MoL) was $70.0 \pm 24.1\%$ (Fig. 2).

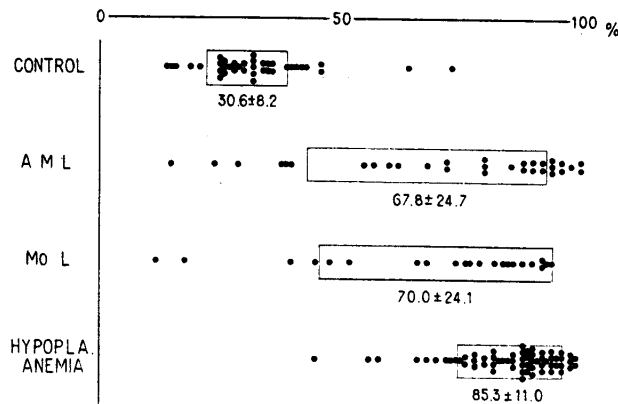


Fig. 2. Incidences of sideroblast

2) *Examinations of the sideroblastogram in HA and AML:*

The pattern of appearance in normal subjects was found to be, as presented in the figure, type 0: $69.4 \pm 8.2\%$, type I: $26.4 \pm 7.7\%$, type II: $4.9 \pm 2.8\%$, type III: 0.8% or less; with statistically significant differences

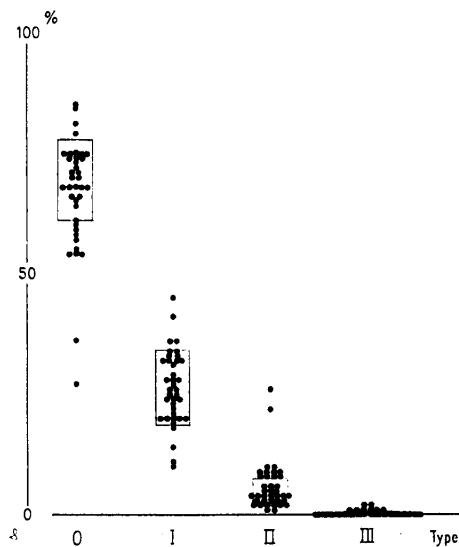


Fig. 3. Sideroblastogram in control, type 0; $69.4 \pm 8.2\%$, type I; $26.4 \pm 7.7\%$, type II; $4.9 \pm 2.8\%$, type III $\leq 0.8\%$

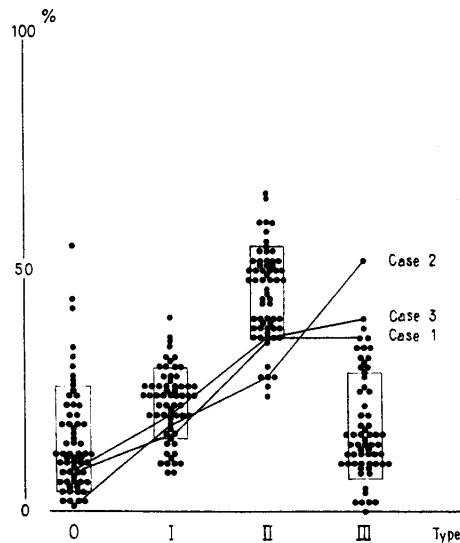


Fig. 4. Sideroblastogram in hypoplastic anemia, type 0; $14.7 \pm 11.0\%$, type I; $22.5 \pm 7.3\%$, type II; $45.0 \pm 9.7\%$, type III $17.7 \pm 10.9\%$

between the types, the sideroblastogram showed a decreasing pattern from type 0 to type III, as a characteristic finding (Fig. 3).

For HA, as shown in the figure, the results were type 0: $14.7 \pm 11.0\%$, type I: $22.5 \pm 7.3\%$, type II: $45.0 \pm 9.7\%$, and type III: $17.7 \pm 10.9\%$, confirming a characteristic pattern of type II sideroblast dominance reported previously (5). The incidence of type II sideroblast dominant cases was very high, being 54 (86.6%) of 63 cases (Fig. 4).

On the other hand, the sideroblastogram in AML was not statistically significant; type 0: $32.2 \pm 24.7\%$, type I: $21.6 \pm 8.3\%$, type II: $31.1 \pm 16.8\%$, and type III: $20.0 \pm 17.6\%$. Type III sideroblast dominance was noted in 5 (15.6%) of 32 cases (Fig. 5). In one (Case 5) of five cases, ringed sideroblasts were present up to 8%.

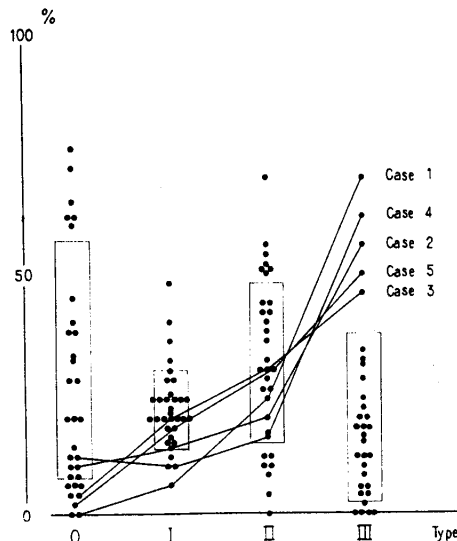


Fig. 5. Sideroblastogram in AML, type 0: $32.2 \pm 24.7\%$, type I: $21.6 \pm 8.3\%$, type II: $31.1 \pm 16.8\%$, type III: $20.0 \pm 17.6\%$

3) Hematological findings in type III sideroblast dominant HA:

The hematological findings in three cases exhibiting type III sideroblast dominance are summarized in the Table. At the time of admission, one case showed reticulocytosis and two cases erythroid hyperplasia in bone marrow. On admission, Case 3 was complicated by an atypical factor, *i. e.* a shift to the left in the granulocytic series and became AML (Table 1).

Sideroblast in Preleukemic Stage

177

TABLE 1 HEMATOLOGICAL FINDINGS OF TYPE III SIDEROBLAST DOMINANT**
CASES IN HYPOPLASTIC ANEMIA

No of Case	Age	Sex	Peripheral Blood				Bone Marrow		My-BI. (%)	Type III Siderobl. (%)
			WBC ($\times 10^3$)	RBC ($\times 10^4$)	Thr. ($\times 10^4$)	Retic. (%)	NCC ($\times 10^4$)	Ery-BI. (%)		
1.	60	F	5.4	266	10.6	?	?	20.4	0.8	36.0
2.	12	M	3.1	251	1.5	24.0	23.7	<u>52.8</u>	0.4	52.0
3.*	55	M	1.5	198	3.8	9.0	11.0	<u>31.8</u>	1.4	40.0

* Left shift of granulocyte series(+), terminated in AML

** 3 of 63 cases, 4.1%

4) Hematological findings of type III sideroblast dominant AML:

Hematological findings in five cases of AML exhibiting type III sideroblast dominance in the sideroblastogram are presented in the Table. Low levels of blasts in the peripheral blood and bone marrow, *i.e.*, identical findings to those in low percentage leukemia, were observed in three cases. The Case 5 was, on admission, considered to belong to the preleukemic stage exhibiting incompletely ringed sideroblasts, and within a few months proved to be low percentage leukemia. About six months later, this case showed erythroid hyperplasia, atypical erythroblasts, PAS-positivity and hiatus erythroleukemia (Table 2).

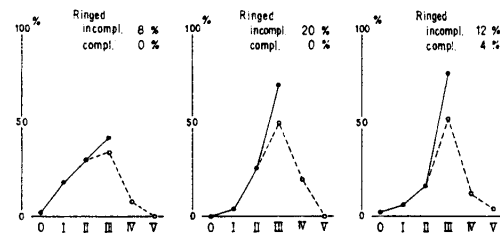
TABLE 2 HEMATOLOGICAL FINDINGS OF TYPE III SIDEROBLAST DOMINANT***
CASES IN ACUTE MYELOCYTIC LEUKEMIA

No of Case	Age	Sex	Peripheral Blood		Bone Marrow			
			WBC ($\times 10^3$)	Blast (%)	NCC($\times 10^4$)	Blast(%)	Erythr.(%)	Type III Siderobl.(%)
1*	67	M	<u>4.3</u>	<u>13</u>	?	<u>14.8</u>	49.6	71
2	57	M	<u>10.7</u>	<u>6</u>	30.3	<u>6.4</u>	25.6	62
3	30	M	88.0	64.0	15.4	68.2	1.6	48
4	39	M	18.3	32.0	67.5	36.2	2.0	70
5*, **	34	M	<u>2.8</u>	<u>0</u>	8.6	<u>5.8</u>	29.4	51

* Megaloblastoid cell(+)

** Ringed sideroblast(+), terminated in erythroleukemia

*** 5 of 32 cases, 15.6%

Low percentage leukemia → Erythroleukemia
Fig. 6. Changes in the sideroblastogram of Case 5

DISCUSSION

Sideroblast is defined as an erythroblast containing stainable iron granules. These granules are known to be non-hemin iron along the iron metabolism of erythroblasts (4). The iron absorbed from the intestinal mucosa is directly used for hematopoiesis and, at the same time, it is stored in the organs as ferritin and hemosiderin, which, when needed, are mobilized to erythroblasts in bone marrow for heme synthesis. In iron metabolism, the erythroblasts play an important role in the course of change from non-hemin iron to hemin iron. Sideroblasts may be considered important for investigating the actual state of iron metabolism. Thus far, numerous reports have been published on sideroblasts; systematic studies on sideroblasts in blood diseases have already been reported by the authors (5).

Numerous reports have been published on PNH, leukemia with a hypoplastic preleukemic stage, hypoplastic leukemia and low percentage leukemia, which should be differentiated from HA; and differentiation of HA, its analogous diseases and leukemia are clinically interesting problems (6). In our studies of leukemia with a hypoplastic preleukemic stage, we have already instituted as atypical HA group. Among cases of atypical HA, those that showed the presence of atypical factors, *i. e.* erythroblasts in the peripheral blood, erythroid hyperplasia in bone marrow, mild increase of blasts in bone marrow or a shift to the left of the granulocytes, were classified as leukemia in a hypoplastic preleukemic stage. If HA should include not only leukemia but also other diseases, this atypical HA group should draw attention (2).

We have re-examined the sideroblasts in HA and AML, and studied the question as to whether or not type III sideroblast dominant cases on the sideroblastogram can be clinically regarded as atypical cases. The incidence of sideroblasts in HA and AML was $85.3 \pm 11.0\%$ and $67.8 \pm 24.7\%$, respectively, while it was $30.6 \pm 8.2\%$ in the control group. Sideroblasts are found during the dynamic course of hemoglobin synthesis from non-hemin iron (7), and the appearance of sideroblasts is influenced by serum iron, *i. e.*, by the supply of iron from the serum and by hematopoietic function. In HA and AML whereby erythropoietic function is low, the high appearance of sideroblasts can be easily explained. In AML, the appearance of sideroblasts is higher than in the control group, but is less uniform and shows a greater statistical variance than in HA. This is believed to occur since the erythropoietic damage in AML is mainly due to displacement of granulocytes by tumorous proliferation, the incidence of granulocyte is not uniform, and latent hemorrhage and infection are more frequent.

Our study on sideroblastograms has confirmed that type II sideroblast

dominance in HA is a characteristic pattern (5). On the other hand, the incidence of type III sideroblast dominant cases was very low, being only three (4.1%) of 63 cases. The question is as to whether or not such cases can be regarded as atypical. Examination of the blood picture on admission showed, as already mentioned, the presence of reticulocytosis, erythroid hyperplasia in bone marrow and a shift to the left in the granulocytic series, indicating hematologically atypical factors. Especially noteworthy is that one of three cases became AML during its clinical course; retrospectively, this case was leukemia with a hypoplastic preleukemic stage. From this finding, cases among HA with type III sideroblast dominance on the sideroblastogram will require clinical follow-up and pathologic analysis as cases of atypical HA. Examining 53 cases exhibiting a preleukemic state, we reported that many of these cases showed erythroblastic damage as seen in HA (frequent incidence of erythroid hyperplasia in bone marrow), pernicious anemia and sideroblastic anemia (3). Subsequently, we have watched erythroblastic kinetics carefully prior to definite diagnosis of leukemia. The fact that pernicious anemia and sideroblastic anemia are representative diseases with type III sideroblast dominance and one of three cases with type III sideroblast dominance became AML seems to have important implications for the preleukemic state.

On the other hand, in AML no such characteristic pattern is observed as in HA nor any significant difference in the incidence of different types of sideroblast. Thus, it may be difficult to pick up atypical cases in AML on the basis of sideroblastograms. We, however, want to draw attention to the fact that three of five cases with type III sideroblast dominant cases turned out to be of low percentage leukemia, and that one of these three cases was, in the early stage, considered to belong to the preleukemic stage exhibiting incompletely ringed sideroblasts and, in the terminal stage, showed erythroleukemia. As pointed out, leukemia with a hypoplastic preleukemic stage is a pathologic state that is potentially leukemic and is essentially different from HA; from a hematological viewpoint we have also pointed out the relationship between leukemia with a hypoplastic preleukemic stage and atypical types of leukemia (hypoplastic leukemia and low percentage leukemia). An increase in type III sideroblasts may be significant with regard to the erythroblastic series in both diseases, *i. e.* leukemia and HA; this demands many more cases to be studied. Changes in the sideroblastogram of Case 5 (low percentage leukemia followed by erythroleukemia) are presented in Fig. 6. Ringed sideroblasts, unlike non-ringed, are believed to be due to disturbed ALA and heme synthetases (9), and are characteristic for sideroblastic anemia. Ringed sideroblasts, however, have been also observed in erythremia and erythroleukemia indicating

relationship between the tumorous proliferation of erythroblasts and disturbed heme synthesis (10). Such cases are extremely rare, and many provide useful informations for the study on the relationship between sideroblastic anemia, Di Guglielmo syndrome and leukemia.

Acknowledgement: The authors express their thanks to Prof. Kiyoshi HIRAKI for advice in the present studies and for a critical review on this paper.

REFERENCES

1. TAKAHASHI, R. *et al*: On the relationship of paroxysmal nocturnal hemoglobinuria and hypoplastic anemia. *The Jap. J. of Clinical Hematology* **9**, 695-704, 1968 (in Japanese)
2. TAKAHASHI, I. *et al*: Clinical investigation on leukemia with hypoplastic preleukemic stage. *ibid* **12**, 61-67, 1971 (in Japanese)
3. KITAJIMA, Y. *et al*: Atypical leukemia. *Jap. J. of Clinical Medicine* **30**, 105-111, 1972 (in Japanese)
4. KAPLAN, E. *et al*: Sideroblasts, A study of stainable nonhemoglobin iron in marrow normoblasts. *Blood* **9**, 203-213, 1954
5. KIMURA, I.: Studies on sideroblasts. Vol. 1, Blood diseases and sideroblasts. *Journal of Med. Association of Okayama* **69**, 1173-1198, 1957 (in Japanese)
6. TAKAHASHI, I. *et al*: Preleukemic states. *Medical Journal of Kawasaki Hospital* **2**, 45-66, 1969 (in Japanese)
7. HIRAKI, K. and KIMURA, I.: Physical significance of the development of sideroblasts and siderocytes and its clinical application. *Jap. J. of Clinical Medicine* **19**, 287-294, 1961 (in Japanese)
8. TAKAHASHI, I. *et al*: Clinical studies on leukemia with hypoplastic preleukemic stage in Japan. *Acta Hematologica Japonica* (in press) (in Japanese)
9. BROWN, W.D.: Abnormal (ringed) sideroblasts in various hematologic and non-hematologic disorders. *Blood* **18**, 662-671, 1961
10. NAKAYAMA, S. *et al*: A case of acute leukemia, associated with sideroblastic bone marrow and termed in erythroleukemic picture. *The Jap. J. of Clinical Hematology* **13**, 50-57, 1973 (in Japanese)