

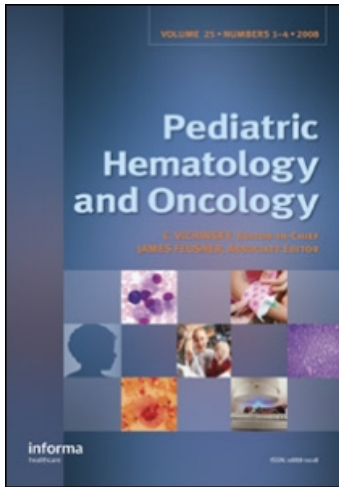
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### DYSPLASIA AND DISORDER OF CELL MEMBRANE ENTIRETY IN IRON-DEFICIENCY ANEMIA

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## DYSPLASIA AND DISORDER OF CELL MEMBRANE ENTIRETY IN IRON-DEFICIENCY ANEMIA

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□ *Peripheral blood smears of 43 patients (26 males, median age 18 months, range: 6–180 months) with nutritional iron-deficiency anemia (IDA) were examined for the presence of trilineage hematological dysplasia. Twelve patients were reexamined for dysplastic findings after achieving a normal Hb and hematocrit level for age by the end of 2–3 months of iron treatment. A control group of 17 age-matched healthy children were also included. Neutrophils with loss of membrane entirety and protrusions were remarkable in 34/43 (79%) in the IDA group versus 1/12 (8%) after iron treatment and none of the control group. Microspherocytes were seen in 9/43 (21%) of IDA patients. Additionally, trilineage dysplasia was observed in the bone marrow samples available in 3 of the patients. It has been shown that iron-deficiency results in cellular DNA and RNA alterations, cell-cycle G1/S phase arrest, and apoptosis. Rac GTPases have been shown to control actin cytoskeleton, influencing cell polarity, microtubule dynamics, and the cytoskeletal organization of hematopoietic cells. Thus, the findings described above in neutrophils and red cells suggest a plausible link between iron and the Rac GTPase gene family. It may be a new avenue for iron waiting for proof.*

**Keywords** anemia, dysplasia, iron

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Dr. Yetgin designed the research; Dr. Yetgin, Dr. Aslan, Dr. Unal, Dr. Elmas, Dr. Kuskonmaz, Dr. Tavail, Dr. Olcay, and Dr. Çetinkaya gathered and analyzed data; Dr. Yetgin, Dr. Unal, and Dr. Tavail wrote the paper.

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Iron is a critical nutritional element essential for biological processes, including hematopoietic cell growth and differentiation and gene-expression regulation [1–3]. Iron-deficiency anemia (IDA) is a systemic disorder affecting multiple organ systems in the body. Marked red cell morphologic abnormalities on peripheral blood smear examinations is one of the principal findings of this disease. Neutrophil hypersegmentation, thrombocytopenia has been reported in IDA [1, 2, 4]. Myelodysplasia represents not only neoplastic hematopoiesis in myelodysplastic syndrome (MDS), but also non-neoplastic one in several hematologic disorders. MDS is a multistep process in which several critical defects accumulate and result in clonality and overt cancer [5–7]. MDS can also be polyclonal, and mitochondrial cytopathies may be a model of polyclonal MDS [6, 8]. Most of these polyclonal MDS cases remit spontaneously. In patients with mitochondrial cytopathy-associated MDS, progression to acute leukemia has not been previously described.

Abnormalities of myeloid hemopoietic cells in IDA, such as neutrophil hypersegmentation and also dysmorphic findings in red blood cells, might be termed as myelodysplasia. These findings also suggest a plausible link between IDA and myelodysplasia. In our clinic we had an experience in a patient with severe IDA who was referred to our center with a possible diagnosis of MDS because of severe dysplasia and anemia. This index case and few previous reports on dysplastic findings, such as neutrophil hypersegmentation and thrombocytopenia in IDA patients, challenged us to examine dysplastic findings in IDA. By this rationale, we examined the hematologic morphology in patients with IDA on a larger perspective. On the basis of the dysplastic hematopoiesis, we observed trilineage dysplasia on peripheral blood and bone marrow (BM) smear examinations in IDA patients.

## MATERIALS AND METHODS

For the purpose of this study 43 patients with IDA were selected. The IDA group consisted of 26 male and 17 female children with a median age of 18 months (range: 6–180). Patients having any infection at the time of or just before the study or chronic diseases other than IDA, malnutrition, and positive bleeding history were excluded from study. Serum vitamin B<sub>12</sub>, folate, zinc levels, and fecal blood were assessed and found to be normal in all of the patients included in the study. The presence of  $\beta$ -thalassemia trait was excluded by evaluation of parental blood count values. IDA diagnosis was based on hemoglobin (Hb), mean corpuscular volume (MCV), red cell distribution width (RDW), serum iron (SI), serum iron binding capacity (SIBC), transferrin saturation (TS), and ferritin values that were compatible with IDA according to the age of the patient together with the presence of microcytic hypochromic red cells on the peripheral blood smear. Peripheral blood smears were examined for the presence of trilineage hematological

dysplasia. Twelve patients could be reexamined for dysplastic findings after achieving a normal Hb and hematocrit level for age by the end of 2–3 months of iron treatment.

A control group of 17 healthy children at the same age with normal Hb and red cell indices were also included in the study to compare dysplastic hematologic findings with the IDA group.

The blood count was performed with a Coulter HmX hematology analyzer. Serum iron, iron binding capacity, and ferritin levels were analyzed by D-mode spectrophotometric analysis. The neutrophil examinations were performed on Wright-stained peripheral blood smears. The two experienced morphologists evaluated dysplastic findings by the aid of a multi-headed microscope, concomitantly with strict criteria. The percentage of dysplastic findings was determined counting 100 neutrophils.

The neutrophils were examined for cell size, hypersegmentation (5 or more lobe in neutrophils) bizarre nuclei (nuclei with projections, such as hook, club, tag, or microlobe, and pseudo Pelger–Huet-like appearance) and cytoplasmic findings (hypogranularity or agranularity, asymmetrical distribution of granules, cytoplasmic area without granules with darker color, and protrusion from cell membranes or cells that had lost the membrane entirely). Giant platelets were assessed by evaluation at 10 subsequent microscopic areas. Red cell morphology were also recorded.

In 3 patients with IDA in whom bone marrow aspiration have been done, BM morphology could also be evaluated for the presence of myelodysplasia.

## RESULTS

Patient characteristics, red cell indices, platelet and leukocyte counts with differential ratios of control, and the IDA group before and after iron treatment are summarized in Tables 1a and 1b. When compared to the IDA group before treatment, Hb and hematocrit values were significantly higher and within the normal range in IDA group after treatment ( $n = 12$ ), but MCV and RDW values were still within IDA ranges. Platelet count was also significantly decreased after iron treatment. Mean and range of SI ( $26.3 \pm 16.4$ ; 1–31  $\mu\text{g/dL}$ ), SIBC ( $418.4 \pm 87.3$ ; 280–550  $\mu\text{g/dL}$ ), and serum ferritin ( $4.1 \pm 5.4$ ; 1–14  $\text{ng/mL}$ ) values were within the IDA limits in patients before initiation of treatment. Serum vitamin B<sub>12</sub> ( $536.3 \pm 285.5$ ; 225–1250  $\text{pg/mL}$ ), folate ( $15.1 \pm 5.8$ ; 3.8–20  $\text{ng/mL}$ ), and zinc ( $51.3 \pm 7.4$ ; 42–60  $\mu\text{g/dL}$ ) levels and fecal blood examination were normal in the IDA group of patients included in the study.

### Peripheral Blood Dysmorphism

In addition to anisocytosis and poikilocytosis, spherocytic red cells were determined in 9 of 43 (20%) patients at peripheral blood smear examinations, although it was not seen in the control group. Neutrophils with

**TABLE 1a** The Characteristics and Hematological Parameters of the Patients in the IDA Group Before and After Treatment and in the Control Group

	IDA <sup>a</sup> group before treatment (n = 43)			IDA group after treatment (n = 43)			Control group (n = 17)		
	Mean ± SD	Range		Mean ± SD	Range		Mean ± SD	Range	
Age (months)	33.5 ± 45.6	6–180		33.5 ± 45.6	6–180		51.3 ± 31.1	6–180	11–108
Gender (female/male)	17/26			17/26			7/10		
Hb (g/dL)	8.7 ± 1.4 <sup>b*</sup>	5.8–10.3		12.5 ± 1.2	11.5–15.0		12.9 ± 0.9 <sup>d*</sup>	11.5–14.0	11.5–14.0
Htc (%)	27.6 ± 3.7 <sup>b*</sup>	19.7–30.9		37.5 ± 3.2	31.6–44.2		37.7 ± 2.4 <sup>d*</sup>	35.6–42.7	35.6–42.7
MCV (fL)	59.0 ± 6.9 <sup>b*</sup>	48.5–74.6		74.7 ± 7.7	70.5–88.5		81.5 ± 4.0 <sup>d*</sup>	72.0–86.9	72.0–86.9
RDW (%)	19.4 ± 3.8	14.2–31.6		20.2 ± 6.9 <sup>c**</sup>	11.9–34.9		12.5 ± 0.9 <sup>d*</sup>	11.6–14.6	11.6–14.6
WBC (×10 <sup>9</sup> /L)	10177 ± 4057	4900–15000		8947 ± 2552	2100–14700		9188 ± 3620	4800–16300	4800–16300
Platelet (×10 <sup>9</sup> /L)	431.7 ± 173.1 <sup>b**</sup>	144–784		351.0 ± 105.1	146–614		325.2 ± 74.9 <sup>d**</sup>	233–371	233–371
PMNL (%)	37.4 ± 16.4	11.0–65.0		38.1 ± 13.5	26.0–62.0		43.8 ± 16.4	21.0–64.0	21.0–64.0
Lymphocytes (%)	53.0 ± 16.9	15.0–64.0		54.2 ± 13.6	23.0–63.0		48.1 ± 17.0	22.0–63.0	22.0–63.0
Monocytes (%)	7.6 ± 3.5	2.0–17.0		6.3 ± 2.6	2.0–12.0		6.6 ± 4.1	2.0–13.0	2.0–13.0
Eosinophils (%)	2.0 ± 2.6	0.0–15.0		0.9 ± 1.3	0.0–4.0		1.5 ± 1.4	0.0–3.0	0.0–3.0

See Table 1b for footnotes.

**TABLE 1b** Laboratory Data of the IDA Group

		IDA <sup>a</sup> group ( <i>n</i> = 43) before treatment					
	Serum iron ( $\mu\text{g/dL}$ )	Total iron binding capacity ( $\mu\text{g/dL}$ )	Ferritin ( $\text{ng/mL}$ )	Vitamin B <sub>12</sub> ( $\text{pg/mL}$ )	Folate ( $\text{ng/mL}$ )	Zinc ( $\mu\text{g/dL}$ )	Blood in stool
mean $\pm$ SD,	26.3 $\pm$ 16.4,	418.4 $\pm$ 87.3,	4.1 $\pm$ 5.4,	536.3 $\pm$ 285.5,	15.1 $\pm$ 5.8,	51.3 $\pm$ 7.4,	—
range	1–31	280–550	1–14	220–1250	3.8–25	42–60	

<sup>a</sup>Iron-deficiency anemia.<sup>b</sup>Comparison between IDA group before and after the treatment.<sup>c</sup>Comparison between IDA group after the treatment and the control group.<sup>d</sup>Comparison between IDA group before the treatment and the control group.\**p* < .001; \*\**p* < .05.

bizarre nuclei were present in 76.7% of the IDA group before treatment, but only 33 and 30% of the IDA group after iron treatment and the healthy group were found to have bizarre nuclei, respectively, and the difference was statistically significant ( $p < .05$ ). Neutrophil hypersegmentation was determined in 67.4% of children in the IDA group before treatment versus 33.3% after treatment and 23.5% in the control group. The finding of dysplastic nuclei with 3 lobes has been observed in eosinophils of IDA group (3 of 43, 6.9%). Cytoplasmic abnormalities (hypo- or agranularity, asymmetrical granule distribution, blue agranular cytoplasmic area, and cytoplasmic protrusion by the loss of cell membrane entirety) were also higher in the IDA patient group than in the group of patients treated for anemia and the normal controls ( $p < .05$ ).

The comparison of dysplastic findings by 100 neutrophil count between IDA and normal control group yielded significantly higher ( $p < .05$ ) dysplastic findings in IDA group in the following parameters: hypersegmentation ( $1.3 \pm 1.5$  versus  $0.4 \pm 0.5$ ), bizarre nuclei ( $2.1 \pm 1.2$  versus  $0.85 \pm 1.3$ ), cytoplasmic abnormalities ( $1.2 \pm 1.8$  versus  $0.1 \pm 0.4$ ), membrane protrusion by the loss of cell membrane entirety ( $3.2 \pm 3.8$  versus 0). Giant platelets ( $0.8 \pm 0.4$  versus  $0.2 \pm 0.4$ ) and thrombocytosis were other findings of dysplasia ( $p < .005$ ) (Table 2).

**TABLE 2** Comparison of the Rate of Patients with Myelodysplastic Features in the IDA Group Before and After Treatment and in the Control Group

Parameters	IDA <sup>a</sup> group before treatment		IDA group after treatment		Control group	
	( <i>n</i> = 43)	%	( <i>n</i> = 12)	%	( <i>n</i> = 17)	%
Nucleus findings						
Hypersegmentation (5 or more lobes)	29 <sup>b*</sup>	67.4	4 <sup>c*</sup>	33.3	4/17 <sup>d*</sup>	23.5
Bizarre nucleus (nucleus with projections, hooks, clubs, tags or microlobes, and Pelger-Huet abnormality)	33 <sup>b*</sup>	76.7	4 <sup>c**</sup>	33.3	5/17 <sup>d*</sup>	29.4
Cytoplasmic findings						
(Hypo or agranulation and granule distribution abnormality)	20 <sup>b**</sup>	46.5	3 <sup>c*</sup>	25	1/17 <sup>d*</sup>	14.3
Membrane abnormality	34 <sup>b*</sup>	79.1	1 <sup>c*</sup>	8.3	0/17 <sup>d*</sup>	–
Giant thrombocytes	35 <sup>b*</sup>	81.4	5 <sup>c**</sup>	41.6	4/17 <sup>d*</sup>	23.5
Erythrocyte abnormality (microspherocytes, poikilocytosis)	9 <sup>b*</sup>	20.9	0	–	0/17	–

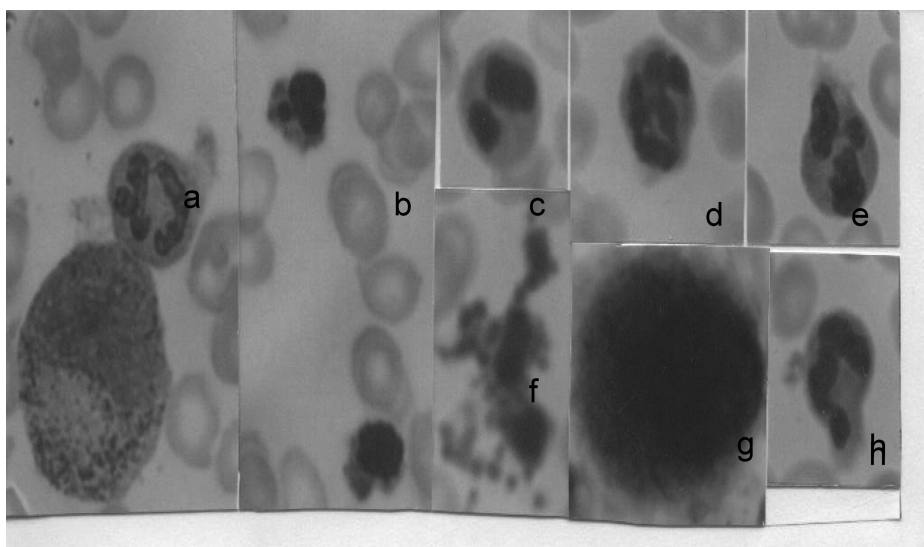
<sup>a</sup>Iron-deficiency anemia,

<sup>b</sup>Comparison between IDA group before and after treatment.

<sup>c</sup>Comparison between IDA group after treatment and the control group.

<sup>d</sup>Comparison between IDA group before treatment and the control group.

\* $p < .001$ ; \*\* $p < .05$ .



**FIGURE 1** Dysplastic changes are summarized: a, d, e, h: membrane protrusion, loss of membrane entirety; b: dysplastic nuclei of normoblasts; c: Pelger-Huet anomaly; d: hypersegmentation in neutrophil; f: giant platelets; g: micromegakaryocyte.

### BM Dysmorphism

Dysplastic changes were especially prominent in erythroid precursors and megakaryocytes. Abnormal nuclei such as bilobed, three-lobed, or irregular form and megaloblastoid normoblasts were also determined. Megakaryocytes were found to be increased and multiple micromegakaryocytes were observed. Dysmorphic findings of the myeloid lineage, such as cytoplasmic hypogranulation and asymmetrical granule distributions, were also present, but they were not as striking as that of erythroid and megakaryocytic dysplasias.

In Figure 1, some of the impressive dysplastic findings of IDA patients are illustrated.

### DISCUSSION

This study presents the dysplastic hematological changes in peripheral blood and BM of IDA patients. Myelodysplastic changes refer to abnormal morphology of the BM and/or peripheral blood and this feature is commonly seen in MDS. Myelodysplasia in peripheral blood and BM can also be seen in different conditions such as autoimmune diseases, infections, especially viral infections, immunosuppressive drugs, chromosomal abnormalities, and DNA abnormalities [9–20]. Iron deficiency results in cellular metabolic enzyme changes, alterations in cellular growth, DNA, RNA, and protein structure, and also increased susceptibility to infections



[1, 2, 21]. Hypersegmentation has been reported in IDA patients previously [22], and in the present study additional dysplastic findings other than hypersegmentation were reported.

Patients included in the study answered questions about infection, any other comorbid disease, drug administration, and vitamin B<sub>12</sub> and folate deficiency. Giant platelets were not related to an associated autoimmune disease [13] or bleeding history and the patients were also examined for the presence of blood in the stool, which may cause consumption of platelets.

Iron deficiency results in dysplastic abnormalities of nails, hair, and skin, in which the cells have an enormous proliferative capacity similar to hematopoietic cells [23]. DNA defects and cell cycle disorders like G1/S phase cell cycle arrest and apoptosis as opposed to differentiation have been observed after iron deprivation [3, 7]. Iron deficiency may result in incomplete processing of DNA and abnormal morphologic features in the cells with high proliferative capacity. In our study, an interesting finding was the loss of cell membrane entirety resulting in protrusion of cell cytoplasm. Spherocytic red cells were unexpectedly found in IDA patients. Recently, it was shown that Rac1 and Eac2 GTPase deficiency in mice alters actin assembly in red cells and causes microcytic hemolytic anemia with bizarrely shaped microspherocytes. Rac controls actin cytoskeleton, influences cell polarity and motility and microtubule dynamics, and regulates cell survival, G1 cell-cycle progression, and transcription [24]. These findings implies that Rac GTPases interfere with the cytoskeletal organization of hematopoietic cells. By this rationale, our findings of microspherocyte, loss of membrane entirety, and cytoplasmic protrusion of neutrophils might be explained by Rac actions in IDA. This interaction needs to be proved by experimental studies, since iron is involved in gene expression regulation. Dysplastic morphology might be observed in conditions of bone marrow activation such as in hemolytic processes or bleeding. Reticulocyte levels in our patients were not indicative of a hemolytic disease and compatible with nutritional IDA. Erythropoietin levels increase in IDA and we know that erythropoietin may also be involved myelopoietic cell activation in all lineages. This may also be a causative factor of dysplastic morphology.

After IDA treatment peripheral blood smears were also examined in patients in whom Hb levels achieved normal values, whereas MCV and RDW levels were still in IDA ranges. Additionally, although dysplastic findings in peripheral blood were found to be decreased after iron treatment, they were still significantly more prominent than normal controls. This might indicate that dysplasia correction competes with IDA correction.

In MDS, iron status may be a functional deficiency and may explain partly the dysplastic changes. The defects in the steps of heme biosynthesis that occur within the mitochondrion produce sideroblastic anemias. The signal feature of sideroblastic anemia is mitochondrial iron deposition. Sideroblasts show normal iron uptake, but subsequent poor incorporation

into heme. Acquired sideroblastic anemias are much more frequent than the hereditary forms. The refractory anemia with ring sideroblasts (RARS) manifest in both the early and late erythroid precursors. Gattermann et al. [25] described at least two point mutations in mitochondrial DNA of patients with acquired sideroblastic anemia causing respiratory chain dysfunction, thereby impairing reduction of ferric iron to ferrous iron. As far as functional iron deficiency causes the dysplastic findings in these patients, we can also expect to find dysplasia in quantitative deficiencies of iron.

The causal relationship of myelodysplastic changes in IDA may be explained by interaction of multifactors such as cellular metabolic enzyme changes, cell growth and differentiation, and gene expression regulation. The ineffective utilization of folate along with vitamin B<sub>12</sub> may also have an additive effect on the dysplasia observed in IDA.

As far as we know, the detailed trilineage dysplastic features have not been reported in iron-deficiency anemia previously. Our morphologic observation in peripheral blood and BM smears of IDA patients is an additional finding.

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