

Type I Dyserythropoietic Anemia in an Elderly Patient

By Jorge E. Maldonado and Howard F. Taswell

A 58-yr-old woman is described in whom light and electron microscopic studies of bone marrow revealed the typical features of type I dyserythropoietic anemia. This form of anemia may be first diagnosed late in life, and caution should be exerted to avoid its confusion with preleukemia or erythroleukemia.

MOST "CONGENITAL" dyserythropoietic anemias are diagnosed early in life (first to third decades).¹⁻³ Recently, we saw a 58-yr-old woman whose initial diagnosis was preleukemia; however, combined light- and electron-microscopic study permitted an appropriate diagnosis of type I dyserythropoietic anemia,⁴ a nonmalignant disturbance of erythropoiesis.

REPORT OF A CASE

A woman born in September 1912 was examined at the Mayo Clinic in March 1971. She had a history of chronic anxiety state and functional fatigue. For at least 35 yr she had been mildly anemic, and various treatments given elsewhere, including iron, liver extract, and vitamin B₁₂, had not helped her. Fifteen years before her present admission she had had a bone marrow study that was interpreted as "suggestive of pernicious anemia." The family history was negative for blood dyscrasias. A cholecystectomy had been performed in 1955 for cholelithiasis; she was not jaundiced. Her breasts had been removed, one 15 and one 18 yr before, because of cancer; no recurrences were noted.

Results of the physical examination were not remarkable, except for atrial fibrillation. The spleen and liver were not palpable.

The hemoglobin level was 10.8 g/dl; erythrocyte count was 3,010,000/cu mm, and leukocyte count was 6400 cu/mm, with a normal differential count. The platelet count was 216,000 cu/mm, and the reticulocyte count was 2.1%. Marked anisopoikilocytosis, with significant oval macrocytosis and prominent basophilic stippling, was seen on a peripheral blood smear. Free gastric hydrochloric acid was present. The serum levels of vitamin B₁₂ and folate were normal. The serum iron level was 117 µg/dl, and the total iron-binding capacity was 169 µg/dl, with 69% saturation. Between 1971 and December 1973, the patient did well, and the hemoglobin level has remained stable.

RESULTS

Serologic Studies

Results of an acidified serum test, performed in October 1973, using serum from eight normal donors as well as the patient's own serum, were negative. Results of an acidified serum test with added thrombin and the sucrose test also were negative. The patient's serum was negative for anti-I, and Ii antigens were present in normal amounts on the patient's erythrocytes.

From the Hematologic Electron Microscopy Laboratory and Blood Bank, Mayo Clinic and Mayo Foundation, and Mayo Medical School, Rochester, Minn. 55901.

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Address for reprint requests: Dr. Jorge E. Maldonado, Mayo Clinic, Rochester, Minn. 55901.

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Bone Marrow Studies

Light microscopy. The bone marrow was hypercellular, with a pronounced increase in erythropoiesis. Binucleated and trinucleated forms were frequent, and there were other cells showing suggestion of division of the nucleus in two or more segments linked by an indented or bridged area. Visible with conven-

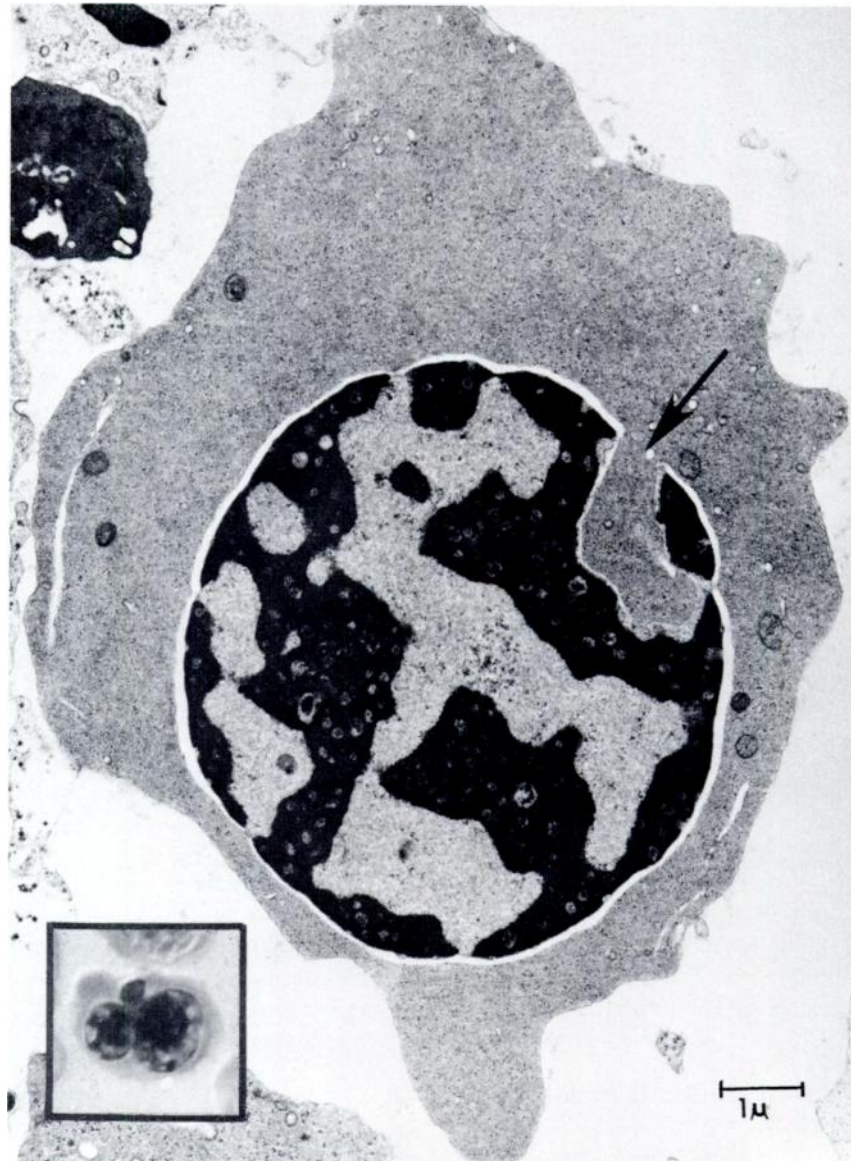


Fig. 1. Normoblast with characteristic features of type I dyserythropoietic anemia. Note "spongy" appearance of nuclear chromatin. Nuclear pore (arrow) is widely dilated and permits penetration of cytoplasm into nucleus. Inset, trinuclear normoblast viewed with interference Nomarski optics. (Wright's stain.)

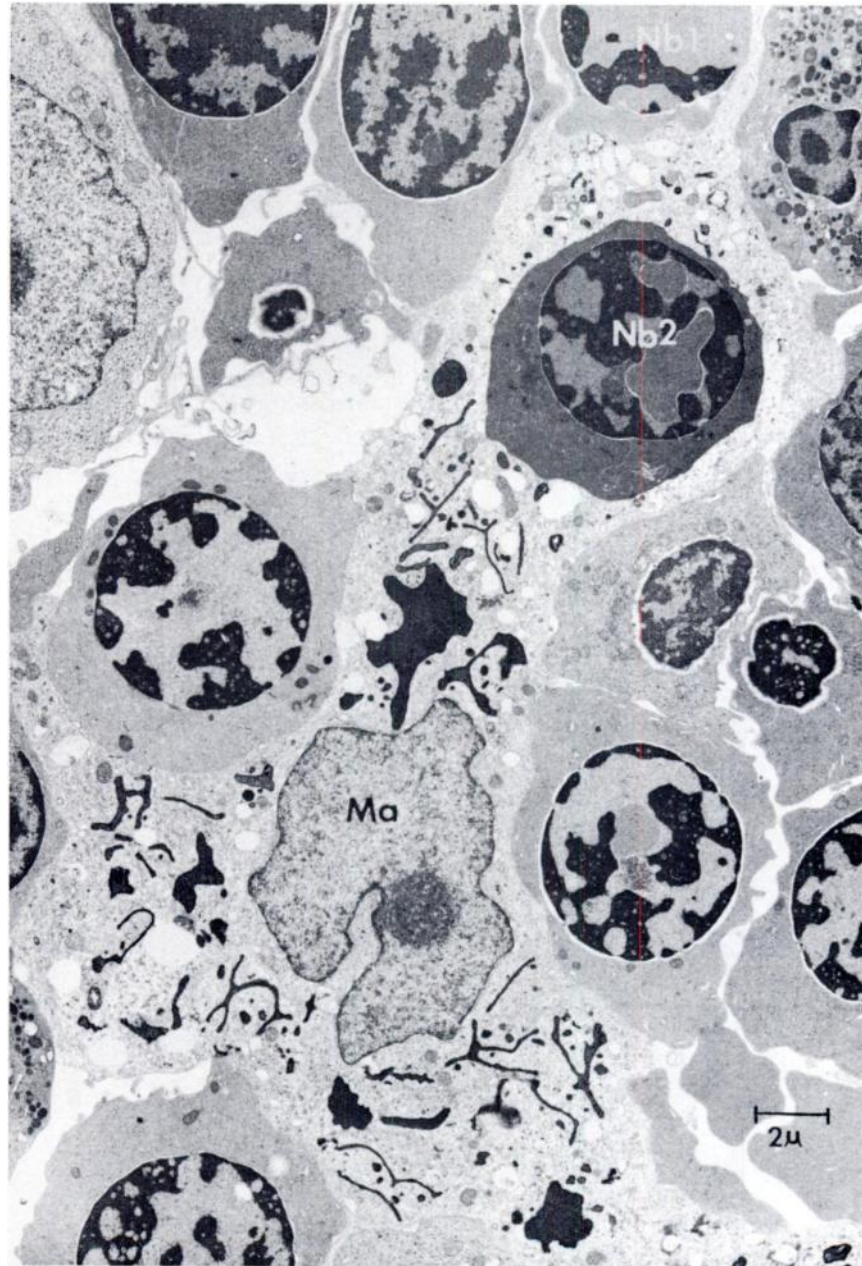


Fig. 2. Center of field is occupied by macrophage (Ma) containing large amounts of hemosiderin and a normoblast (Nb2), which has been phagocytosed. Several other normoblasts of various stages of development are seen. One of them (Nb1) shows marked disarray of nuclear structure.

tional light microscopy but more evident with interference Nomarski optics was a "porosity" of the nuclear structure, with cytoplasmic (hemoglobin) penetration into the nucleus (Fig. 1 inset). The granulocytic series and the megakaryocytes were not remarkable. Many mast cells and numerous iron-laden macrophages, as well as increased intracytoplasmic iron in the red cell precursors, were seen.

Electron microscopy. Immediately after aspiration, the bone marrow spicules were immersed in 3% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3) and fixed for 3 hr at room temperature. Subsequently, fixation in 2% osmium tetroxide for 1 hr at 4°C and postfixation stain "in block" with uranyl acetate (0.5% in water) for 1 hr were done and the tissues embedded in epoxy resin. The sections were double stained with uranyl acetate (15–20 min) and lead citrate (2½ min) and viewed with an electron microscope (Hitachi HU-12).

Conspicuous abnormalities of the erythrocytic precursors were present (Figs. 1–3). The changes were similar to those previously reported by others⁴⁻⁶ and

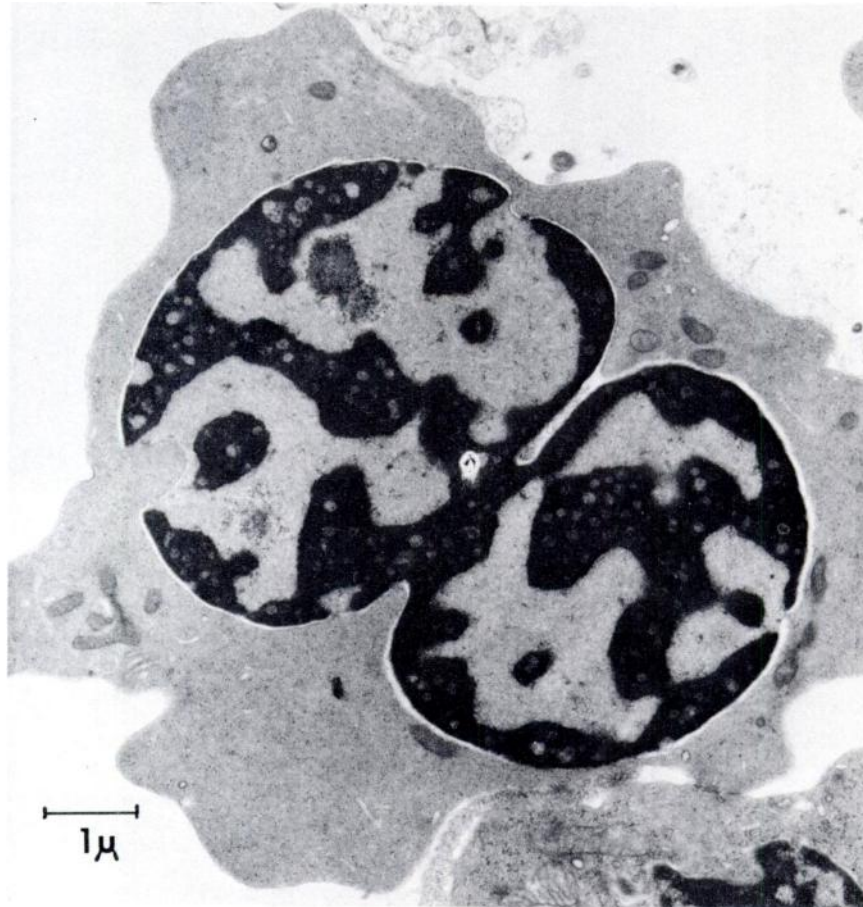


Fig. 3. Normoblast with two nuclear segments. Note the "spongy" appearance of the nuclear chromatin.

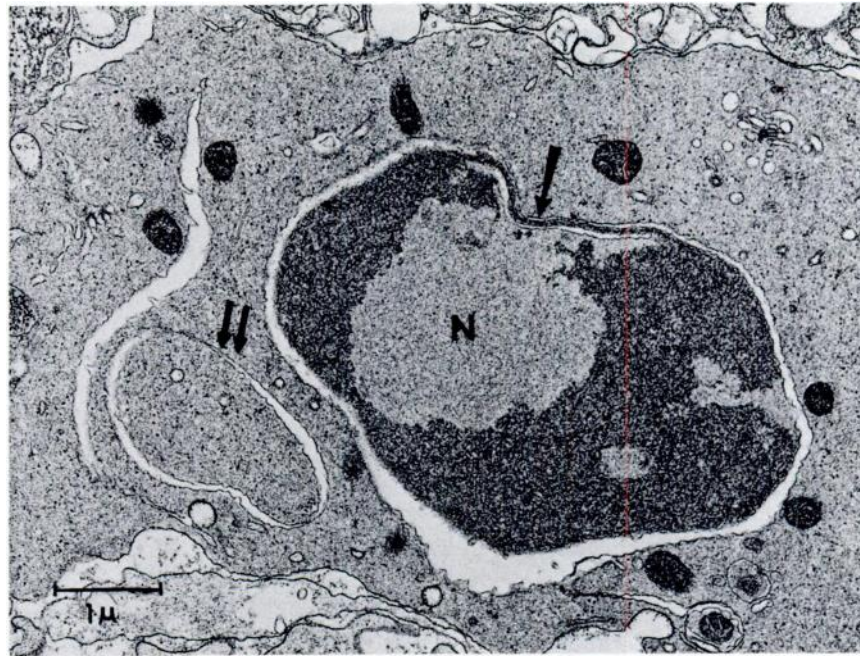


Fig. 4. Central area of normoblast showing duplication of nuclear envelope (single arrow) and lamellae of endoplasmic reticulum or remnants of duplicated nuclear or cellular membranes (double arrows). N, nucleus.

included aberrations of nuclear and cytoplasmic structures. The nucleus was often of irregular contour, having a “sausage-like” configuration (Fig. 3), or there were two or more nuclei or nuclear segments linked by nuclear bridges.⁴⁻⁶ Irregularities or a tendency to duplication of the nuclear contour was even seen in very early precursors (Fig. 4). In some instances, the nucleus was completely disorganized, with disappearance of large segments of the nuclear envelope (Fig. 2). In many other instances, only wide nuclear pores were present, with clear-cut penetration of the cytoplasm into the nuclear area (Fig. 1). The chromatin pattern had a “porous” or “spongy” appearance, resulting from the cross section of widely opened nuclear pores. This appearance is characteristic of type I dyserythropoietic anemia.

The perinuclear space occasionally was dilated (when adjacent nonerythrocytic cells had narrow perinuclear space), and myelin figures occupied segments of this space.

The mitochondria often had accumulation of iron, and they were sometimes short or plump. The morphologic appearance of these iron-laden mitochondria is different from that seen in the more common type of refractory sideroblastic anemia in which the mitochondria are frequently dilated and have evidence of degenerative changes. Occasionally, siderosomes were seen, and ferritin granules were abundant in the cytoplasm. Cytoplasmic microtubules and lamellae of endoplasmic reticulum were frequently seen.

There were abundant macrophages loaded with hemosiderin and ferritin,

often exhibiting phagocytosis of normoblasts in various degrees of degeneration (Fig. 2). Nuclear blebs were frequently seen in granulocytic cells. Ultrastructural abnormalities of the circulating erythrocytes were not detectable.

DISCUSSION

The light- and electron-microscopic findings of the erythrocytic lines in this patient are typical of type I dyserythropoietic anemia. Results of serologic studies are in keeping with this classification.

The congenital, or perhaps better designated, constitutional dyserythropoietic anemias are rare disorders. This is particularly true of type I, which has a negative acid hemolysis test, normal amounts of I and i antigens, and no agglutination with anti-i or lysis with anti-i or anti-I. Type II or HEMPAS (hereditary erythrocytic multinuclearity with positive-acidified serum) is a more common disorder.

Type I dyserythropoietic anemia is compatible with long life, as demonstrated by our patient and by a 76-yr-old woman recently described by Bethlenfalvay.⁷ In our patient, the megakaryocytes were morphologically normal, in contrast with the patient of Bethlenfalvay, who was reported to have 40% abnormal megakaryocytes. This type of dyserythropoiesis might be confused with the dyserythropoiesis of a malignant involvement of the red cell line (for example, erythroleukemia). The nuclear structure, particularly the "spongy" appearance of the nuclear chromatin, permits the differentiation from neoplastic disorders.

A positive family history in dyserythropoietic anemia is helpful in establishing the classification of the disorder as congenital. In type I dyserythropoietic anemia, however, several cases,^{5,6} including ours, have had a negative family history. We prefer the designation of this anemia as simply type I dyserythropoietic anemia or as constitutional (or perhaps idiopathic) when there is no evidence of a familial occurrence of the disease.

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