CASE REPORT

A Case of Erythremic Myelosis (Di Guglielmo)

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In 1923 and subsequently, Di Guglielmo demonstrated by clinical, hematologic and pathologic data the existence of a primitive disorder of the erythropoietic system, similar to the acute leukemias, to which he gave the name of "acute erythremic myelosis."

Until that time, the general opinion had been against the likelihood of such a disorder. In the following years, several cases of this entity were published, all in Europe. However, according to Moeschlin, only five of the cases reported until 1940 "can withstand critical scrutiny." He stated that some of the cases labelled as erythremic myelosis were probably examples of various disorders, including Cooley's anemia. Duesberg, in 1940, and later Di Guglielmo, pointed out that, as in the leukemias, there were cases of erythremic myelosis in which the clinical course was a chronic one.

Briefly, the features of acute erythremic myelosis are, according to Di Guglielmo: severe anemia from the very onset of the disease; irregular fever, frequently remitting in type; splenomegaly, almost always marked; hepatomegaly, not so considerable as the splenic enlargement; an acute clinical course with a duration varying from some weeks to two months; and a fatal termination. Other features include: the presence of numerous erythroblasts in the blood, most of them basophilic and very often atypical (paraerythroblasts); generalized proliferation of the erythropoietic tissue in all the hematopoietic and extrahematopoietic organs; and hemorrhagic manifestations of variable severity.

Regarding the chronic form of the disease, the major differences, as contrasted with the acute variety, are the duration of the clinical course, which averages two years, and the fact that the erythroblasts found in the blood are more mature. Most of them are orthochromatic but a few polychromatic and basophilic forms may be found. It may be said that the clinical picture of erythremic myelosis may be likened to that of the granulocytic leukemias, criteria for differentiation being based solely on the cytologic aspects of the blood and bone marrow.

Other basic characteristics of erythremic myelosis, acute and chronic, have been enumerated by Di Guglielmo: hyperplasia of the erythropoietic tissue

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Submitted May 9, 1953; accepted for publication August 10, 1953.

The authors wish to express their gratitude to Dr. Salvador Aceves (Chief of Clinical Service, Instituto de Cardiología), who made possible the continued study of this patient and the publication of this paper.

Dr. Ignacio González Guzmán, Chief of the Laboratory of Hematology of the Instituto Nacional de Cardiología, has made hematologic and histopathologic studies in connection with this case.
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with such characteristics as primitiveness of a nonregenerative or reactive process; generalized invasiveness; nonreversibility persistent until death and unmodified by therapeutic means; and an embryonic type of maturation stemming directly from reticuloendothelial cells. In a limited sense, erythemic myelosis may be thought of as a disorder of the reticuloendothelial system.

The abnormal erythropoiesis is anaplastic. Maturation of the red cells is arrested and complete evolution to adult forms seldom occurs. This phenomenon is particularly noticeable in the acute type of the disease, since in it there is absence of the intermediate forms of the erythrocytes. Thus there may be a hiatus erythremicus, similar to the hiatus leukemicus of acute granulocytic leukemia. Finally, there is dysplasia of erythropoiesis leading to the presence of abnormalities in the cytoplasm and nuclei of the erythroblasts.

The case which follows presented several interesting features and gave us the opportunity of making a differential diagnosis between acute hemolytic anemia, acute leukemia, and the Di Guglielmo syndrome.

CASE REPORT

An unmarried man, aged 20 years and a resident of a nontropical zone of Mexico, was admitted to the Hospital de Enfermedades de la Nutrición (case 4749) on September 7, 1948.

The onset of clinical symptoms was vague. In August 1947, after an acute episode of amebic dysentery, weakness and shortness of breath appeared which became progressively more intense. Gradually, other symptoms appeared, including pallor, loss of weight, and ankle edema. In May 1948, jaundice was noted with no change in the color of the feces. Coinciding with the jaundice was high fever.

In the following weeks, the jaundice persisted but with less intensity. The temperature remained stationary, averaging 38.4°C. Gradually, hemorrhagic manifestations developed, including petechiae and ecchymoses and profuse epistaxis.

On admission, the patient showed slight jaundice and marked pallor. There was enlargement of the liver, its lower edge being felt 6 cm. below the costal margin in the midclavicular line. It appeared to be firmer than usual. The spleen was not palpable. There was moderate enlargement of the inguinal lymph glands. On the medial surfaces of both legs, superficial ulcerations of the skin without tendency to healing were present.

Hematologic Data

Blood. The findings of the first and the last hematologic examinations will be described. The results of the intermediate examinations are expressed in figure 1. May 31, 1948: Hemoglobin 5.15 Gm. per 100 cc. of blood; erythrocytes 1,820,000 per cu. mm.; volume of packed erythrocytes 18 per cent; mean corpuscular volume 99 cu. µ; M. C. Hb. C. 28; nucleated cells 83,200 per cu. mm.; lymphocytes 2 per cent (1664 per cu. mm.); neutrophils 1.2 per cent (998 per cu. mm.); bands and segmented forms 0.6 per cent; basophilic normoblasts 0.4 per cent (332 per cu. mm.); ortho- and polychromatic normoblasts 96.4 per cent (80,204 per cu. mm.); platelets greatly decreased; reticulocytes 15.4 per cent. Sept 22, 1948 (one day before the patient's death): hemoglobin 3.91 Gm.; erythrocytes 1,140,000 per cu. mm.; volume of packed erythrocytes 13 per cent; mean corpuscular volume 118 cu. µ; M. C. Hb. C. 30; nucleated cells 32,850 per cu. mm.; lymphocytes 2.4 per cent (786 per cu. mm.); eosinophils 0.2 per cent (85 per cu. mm.); neutrophils 2.8 per cent (959 per cu. mm.); myelocytes 0.4 per cent; metamyelocytes 0.2 per cent, band forms 1.0 per cent, segmented 1.2 per cent; pronormoblasts 12.8 per cent (4204 per cu. mm.); basophilic normoblasts 7.0 per cent (2,299 per cu. mm.); ortho- and polychromatic normoblasts 74.8 per cent (26,581 per cu. mm.); platelets greatly decreased; reticulocytes 5.8 per cent.

There was an extreme variation in the size of the red blood cells, which was also present in the normoblasts. Most of the nucleated red cells had a characteristic normoblastic nuclear pattern, although there were many cells with a reticular distribution of the chromatin.
The appearance of the latter cells resembled intermediate forms between the normoblasts and the megablasts. Karyorrhectic forms were very frequent. Occasional naked nuclei and erythrocytes, containing many Howell-Jolly bodies, were also seen.

Pronormoblasts were present in scant amounts during the initial examination and in progressively increasing numbers during the last month of the patient's life. The nuclei of these cells were often deeply lobulated and contained from one to four large and conspicuous nucleoli. Myelocytes were also seen in some of the blood films.

Bone marrow. Two bone marrow punctures were done. On both occasions the slides showed normal cellularity and complete absence of megakaryocytes. In the first examination (May 29, 1948) the erythrogranulopoietic ratio was 12:1, with the following differential red count: pronormoblasts 5 per cent; normoblasts 20 per cent; megaloblast-like cells 75 per cent (these cells had the same intermediate aspect described previously).

The second bone marrow puncture was done three days before the patient's death. The examination of the slides gave the following data: erythrogranulopoiesis ratio 30:1;

Fig. 1.—Findings on hematologic examination. Greater detail on the first and last examinations is given in the text.

pronormoblasts 50 per cent; normoblasts 34.8 per cent; megablast-like cells 12.4 per cent; neutrophils—myelocytes 0.4 per cent, band forms 1.0 per cent, segmented 1.0 per cent; eosinophils 0.4 per cent.

In both examinations, in the group of pronormoblasts, typical and atypical forms were encountered. The atypical forms had a reticulated nucleus which gave the cells the aspect of promegaloblasts. All the blasts showed from one to three, rarely four or five, large and conspicuous nucleoli.

Several striking features were noticeable in the bone marrow slides: the presence of azurophilic granulations in many of the pronormoblasts; lobulation of the nuclei; occasional binucleated normoblasts; asynchronism between the maturation process of the nucleus and the cytoplasm, i.e. cells with polychromatophilic cytoplasm and very primitive nucleolated nucleus; and nests of reticuloendothelial cells with forms intermediate between them and the promegaloblasts.

Hemorrhagic studies. Bleeding time (Duke) 4½ minutes; clotting time of the oxalated plasma on recalcification 150 seconds; prothrombin time (Quick) 20 seconds, (control
PLATE I.

Fig. 2.—Peripheral blood. Initial examinations, when the normoblastic count was very high.

Fig. 3.—Peripheral blood. Final examinations. Type of blasts present.

Fig. 4.—Bone marrow. Initial study. Tetrapolar mitosis of an erythroblast. A primitive cell with a huge nucleolus and several megaloblast-like erythroblasts are also seen in this film.

Fig. 5.—Bone marrow. Initial study. Erythroblasts showing the reticulated pattern of the chromatin and the cytoplasm-nucleus asynchronism.

Fig. 6.—Bone marrow. Final study. Nest of reticuloendothelium cells with definite malignant aspect.

Fig. 7.—Bone marrow. Final study. Very primitive erythroblasts with azurophilic granulation.

14 seconds); tourniquet test negative; platelet count (indirect method) 19,263 per cu. mm.; clot retraction greatly delayed.

Studies of the hemolytic component. Indirect bilirubin 2.20 mg. per cent (June 2, 1948), 0.40 mg. per cent (Sept. 22, 1948); hypotonic fragility of the red blood cells beginning
hemolysis at 0.55 per cent, complete at 0.30 per cent (control 0.45 and 0.30); fecal urobilinogen (Watson) 787.5 mg. in 24 hours. (Average of 3 day determination); urine urobilinogen (Watson) 17.3 mg. in 24 hours. (Average of 3 day determinations).

**Liver Function Tests**

Direct bilirubin 0.40 mg.; bromosulphthalein retention 13 per cent; plasma albumin 3.41 Gm. per cent; plasma globulin 2.95 per cent; total cholesterol 95 mg.; esterified cholesterol 61 per cent; cephalin cholesterol flocculation +++; thymol turbidity 12 units.
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Other Tests and Examinations

Kahn, Eagle, and Mazzini negative; blood uric acid 6 mg. per 100 cc.; urine analysis albumin 1.5 Gm./1000 cc.; electrocardiogram normal; x-ray examination of the thorax negative.

Clinical Course

Following admission, the hemorrhagic manifestations increased and the infections reached great severity, despite the continuous use of penicillin. The hematologic picture remained unchanged.

Finally, on the tenth day, there was circulatory collapse followed by death. The total length of the clinical course was approximately thirteen months.

Pathologic Examinations

An autopsy was performed and the following data were found:

Macroscopic*

The body was that of a fairly well nourished young man of asthenic build. The brain and pia were slightly edematous in appearance. Bilateral pleural effusions were present; there was marked global hypertrophy of the heart with some dilatation of all cavities and without evidence of valvular lesion. The lungs were heavier than normal (781 and 994 Gm.) and showed marked congestion and edema. The liver was increased in size and weight (3223 Gm.) and was light reddish-brown in color and smooth surfaced; liver tissue was soft and friable and the cut surface showed faint yellowish mottling and haziness of the lobular pattern. The kidneys showed a smooth surface spotted by subcapsular hemorrhages; they were large, elastic, and juicy in appearance. The adrenal cortex was brown and compact with few yellowish lipoid deposits.

Bone marrow was abundant and grayish-red. The lymph nodes of all chains examined were increased in size, the largest ones about 4 cm. in diameter. They did not adhere to the surrounding tissue; their capsule was glistening, reddish in colour; on cut surface they showed a pinkish color and friable consistency. Most affected were the paraaortic and pelvic chains. The spleen was only slightly increased in size (219 Gm.) and its gross appearance was normal except for the presence of numerous, hardly visible whitish dots.

Microscopic

Lung: Besides the passive congestion and edema suggested by gross examination, there were widespread areas of hemorrhage. Occasional fields showed intra- and extravascular accumulations of erythroblasts especially around the small sized bronchioles. There were also numerous alveoli full of fibrin threads with inflammatory cells, alternating with other alveoli full of hemorrhage. Within the alveolar capillaries many erythroblasts could also be seen.

Kidney: Gross diagnosis of cloudy swelling was confirmed by the microscopic aspect of the tubules. Abundant small focal hemorrhages were found, together with casts composed of albumin and red cells. In the cortical zone, areas of infiltration were seen; erythroblasts were noted in and out of the blood vessels of this area.

Liver: There was marked centrilobular infiltration of multiple, small fat droplets; the sinusoids showed evident dilatation. Proliferation of Kupffer cells and presence of abundant erythroblasts in the sinusoids were prominent features. Occasional infiltrations of abnormal red cells were found scattered through the sections, showing a superficial resemblance to septic foci or leukemic infiltration, but consisting of erythroblasts.

Spleen: The capsule and trabeculae were normal in appearance. The lymphatic follicles were enlarged, showing hazy outlines and merging into the surrounding pulp. Germinal centers were either absent or replaced by abnormal elements, mostly erythroblasts, i.e.

* All the pathologic studies were done in the Departamento de Anatomía Patológica del Hospital de Enfermedades de la Nutrición, by Dr. F. Lichtenberg.
atypical elements with sprouting and pyknotic nuclei; many germinal centers also showed large acidophilic cells with pyknotic and peripherally displaced nuclei and with many characteristic features of necrobiosis. The periphery of the lymph follicles showed numerous erythroblasts which formed a halo around each of them. The sinusoids and cords of the red pulp were very cellular and the outlines of the latter were difficult to distinguish. Most of the cells were erythroblasts with their sprouting and pyknotic nuclei giving to the pulp a general necrobiotic appearance. Also in the red pulp were abundant large macrophages containing brownish granular pigment which stained blue by Perl’s method for hemosiderin. Most of the macrophages were found to be enlarged and bulging into the cavity. Proliferation of reticuloendothelial cells was evident.

Lymph nodes: The picture was similar in all specimens observed. The general structure was much better preserved than in the spleen. Follicles were somewhat smaller than normal and there was production of erythroblasts in the peripheral zone. However the chief production of erythroblastic cells seemed to take place in the sinusoids which were filled to the limit with abnormal elements. Besides erythroblasts, the sinusoids contained large macrophages with hemosiderin granules in smaller number than in the spleen; occasional eosinophils and megakaryocytes could be observed.

Special Examinations

Imprints of spleen, lymph nodes, and liver were made from postmortem material and stained with Wright’s stain. All of them showed a large number of reticuloendothelial cells, either discrete or clumped in nests. These cells were almost as numerous as those seen in similar preparations of reticuloendotheliosis and Hodgkin’s sarcoma. There were, besides, a great many nucleated red cells in different stages of development and abundant intracellular pigment.

Comment: Differential Diagnosis from Hemolytic Anemia and Acute Leukemia

Di Guglielmo’s erythremic myelosis is rare. Most of the observed cases have been studied in Europe. This probably explains the common acceptance of erythremic myelosis in European countries and the skepticism regarding the disease which appears to be prevalent in North America.

In the differential diagnosis of our case, hemolytic anemia and acute granulocytic leukemia were considered. The existence of abnormal hemolysis was quite evident, as indicated by the presence of jaundice with high amounts of indirect bilirubin in blood, normochromic anemia, reticulocytosis, diminished resistance of erythrocytes to hypotonic solutions, high daily output of fecal urobilinogen, and the erythroblastic bone marrow.

However, chronic hemolytic anemia, either congenital or acquired, could not satisfactorily explain the entire picture in this case:

1. Although normoblasts may be seen in the peripheral blood during the course of hemolytic anemias, they are usually scant. The intensity of the normoblastemia depends on the age of the patient, the severity of the hemolytic phenomena, the existence of ectopic foci of erythropoiesis, and unknown factors, probably of an individual nature. The greatest degree of normoblastemia in hemolytic anemias is seen in erythroblastosis fetalis, in which several of the above mentioned factors may be present simultaneously. In hemolytic anemias of the adult, normoblastemia may be seen during acute crisis and following splenectomy. Figures as high as 200 normoblasts per 100 leukocytes have been reported by Israels,4 but, as he stated, this is rare. Sustained normoblastemia is also rare. In our case there were 2670 normoblasts per 100 leukocytes at the
initial examination and only once in the entire clinical course was this relationship lower than 100 per 100 white cells. Thus, it is quite improbable that our patient had a hemolytic process of a year’s duration so severe as to produce the normoblastemia of the observed magnitude and constancy.

2. Lack of well defined splenomegaly is unusual in hemolytic anemia. The spleen in this case weighed 219 Gm. There is no reported case of chronic hemolytic anemia, either congenital or acquired, with a spleen of normal size and weight at autopsy.

3. Pronormoblasts may be seen in the peripheral blood during intense reactive normoblastemia, but they are characterized by low absolute and relative figures and normal morphology. In this case the primitive cells which appeared in the blood during the final examinations, presented morphologic abnormalities so outstanding that their classification was difficult. The most conspicuous changes were marked indentation of the nucleus and the presence of large nucleoli. These features cannot be explained by a hemolytic disease alone.

As regards leukemia, the presence of 12.8 per cent primitive cells, i.e., blasts in the peripheral blood, the thrombocytopenia, and the 50 per cent blast content of the bone marrow required a differentiation from acute granulocytic leukemia. This case, however, showed atypical features not seen in granulocytic leukemia, either of the acute or subacute variety. These consisted of:

1. Prolonged abnormal erythropoiesis manifested by anemia, very marked normoblastemia, marked increase in erythropoiesis with predominance of the embryonal type of erythropoiesis over the normal one, and the presence of abnormal mitoses. There was no evidence of granulocytic leukemia during this stage which lasted at least three months.

2. Definite hemolytic component from the very onset with no splenomegaly. Everything pointed to a erythrocytic defect as the fundamental cause for the increased hemolysis, with the role of the spleen being secondary.

3. Profound reticuloendothelial proliferation and presence of erythropoietic foci in several organs, without evidence of any leukemic infiltration.

So it is clear enough that this case was not one of hemolytic anemia or of acute leukemia. Instead it can be said that the disorder is indeed one of red cell proliferation, malignant in its course, thus constituting a clear example of one of the “myeloproliferative syndromes,” in which erythremic myelosis is included at the side of chronic granulocytic leukemia, polycythemia vera, and megakaryocytic leukemia.

**SUMMARY**

A case of chronic erythremic myelosis (Di Guglielmo) is presented; the diagnosis was established by clinical, hematologic, and pathologic data. The peculiar characteristics of this particular case are discussed, as well as the differential diagnosis from hemolytic anemia and acute leukemia.

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