Paroxysmal Nocturnal Hemoglobinuria with Acute Leukemia

By Dorothy Holden and Herbert Lichtman

The occurrence of impaired marrow function in paroxysmal nocturnal hemoglobinuria (PNH) has long been recognized. A smaller group of patients, with an initial diagnosis of aplastic anemia, have been noted to develop signs of PNH during the course of their illness. Such persons have been said to have “the aplastic anemia—paroxysmal nocturnal hemoglobinuria syndrome.”

Also evident, in some cases of aplastic anemia, has been the increased production of primitive leucocytes in the bone marrow. The resulting clinical picture is often that of an acute or “stem cell” leukemia.

As a result of the foregoing observations, it has been postulated by Dame-shek that any or all three of these conditions (PNH, aplastic anemia, and “hypoplastic” leukemia) might result from a “common” injury to the marrow.

The following case report is believed to illustrate the occurrence of PNH and so-called acute “hypoplastic” leukemia.

Case Report

M.D., a 37 year old Negro housewife, was first seen in March 1956, with complaints of “weakness and dark urine.”

She had been hospitalized elsewhere with similar symptoms in January 1955. At that time she was also jaundiced and had noted that her urine was “red in the morning.” According to the patient, radiological examination of the genitourinary tract yielded normal results; urinalyses were also reportedly “normal except for the color.” Blood counts were not available and were unknown to the patient. Treatment was said to have been limited to blood transfusions and to the administration of oral iron salts.

During subsequent months similar changes in the color of the urine occurred. Each episode lasted two to three weeks. There had been no recurrence during the summer months.

At age 16, the patient had acute rheumatic fever. Although asymptomatic since, she had been told of a “heart murmur.” Of three pregnancies, the first two ended in spontaneous abortions; the third resulted in the birth of a normal, full-term infant who was alive and well.

The family history was negative.

Physical examination was negative except for the presence of a grade III aortic diastolic murmur and a grade III apical systolic murmur. The mitral first sound was accentuated but no thrills were present.

Peripheral blood counts were as follows: erythrocytes 2.13 million per cu. mm.; hemoglobin 5.8 Gm./100 ml.; hematocrit 20.5 per cent; reticulocytes 2.2 per cent; leucocytes 3,000/cu. mm. The white blood cell differential count revealed 33 per cent

From the Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y.

First submitted July 17, 1968; accepted for publication October 15, 1968.

Dorothy Holden, M.D.: Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y. Herbert C. Lichtman, M.D.: Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y.
segmented neutrophiles, 20 per cent band neutrophiles, 1 per cent eosinophiles, 2 per cent basophiles, 40 per cent lymphocytes and 2 per cent monocytes. Platelets were noted to be normal on examination of the stained peripheral blood film.

Hemoglobinuria was present with no evidence of hematuria. The acidified-serum test was positive when performed according to the method of Ham.4

Additional laboratory data were as follows: Total serum bilirubin 2.2 mg. per cent, direct bilirubin 0.5 mg. per cent; the serologic test for syphilis was negative, the erythrocyte osmotic fragility was normal, and the blood type was group O, Rh positive. The direct and indirect Coombs’ test was negative. The sodium metabisulfite test for sickling was also negative.

A diagnosis of PNH was made. After transfusion with 1000 ml. of whole blood, therapy was instituted with Prednisone 20 mg. daily, oral iron salts and potassium chloride. After the cessation of gross hemoglobinuria, the patient was discharged to the outpatient clinic.

During the following two years several episodes of gross hemoglobinuria occurred. Hemosiderinuria and, occasionally, hemoglobin casts could be detected.

The patient complained frequently of palpitations, nervousness, and of vague epigastric burning pain. X-ray examination of the gall bladder and the gastrointestinal tract was normal.

In May 1960 therapy with prednisone was discontinued, gross hemoglobinuria having not been noted since 1958. The acidified-serum test remained positive until September 1960. Thereafter, results of the test were repeatedly negative.

Because of menometrorrhagia, hospital admission was necessary in November 1960, a diagnosis of uterine fibromyomata was made. Hospitalized again in December 1960, the patient was transfused with three units of compatible packed red cells. On the day following the third transfusion, a total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed under spinal anesthesia. A urine specimen obtained immediately prior to surgery was described as being a “smoky port wine color.” Gross hemoglobinuria, which persisted for four days, was again present. The postoperative recovery period was otherwise uneventful.

The fourth hospitalization occurred in May 1961 at which time a disseminated pyoderma was present. Cultures of the skin lesions, and one of many blood cultures, revealed the organism to be a coagulase-positive Staphylococcus aureus. In addition to the multiple pustular lesions, physical examination revealed the presence of fever, cardiomegaly, and signs of aortic valvular insufficiency and stenosis. Urinalysis revealed only mild albuminuria. Whereas leukopenia had been previously persistent, the white cell count was 13,300/cu. mm. with a differential count of 38 per cent segmented neutrophiles, 29 per cent band neutrophiles, 1 per cent metamyelocytes, 19 per cent lymphocytes, and 13 per cent monocytes.

Following antibiotic therapy the patient was discharged, without symptoms, from the hospital.

She remained apparently well until her admission to the hospital for the fifth time in March 1962. Dental extractions three weeks previously had been followed by excessive bleeding and abscess formation. Therapy with penicillin had been instituted and continued for the ten days prior to hospital admission. On examination the patient was afebrile and significant physical findings were limited to the evidence of recent dental extractions, generalized peripheral lymphadenopathy which was nontender, and the previously described cardiac abnormalities.

The blood picture was as follows: hemoglobin 11 Gm./100 ml., hematocrit 36 per cent, reticulocytes 1.2 per cent, platelets 390,000/cu. mm., leucocytes 11,300/cu. mm. Examination of a Wright’s stained blood film revealed 32 per cent segmented neutrophiles, 15 per cent band neutrophiles, 2 per cent neutrophilic metamyelocytes, 16 per cent lymphocytes, 21 per cent monocytes and 14 per cent “blast” cells with mononucleated nuclei. There was mild polychromasia, anisocytosis and poikilocytosis of the red cells; platelets were noted to be often large and atypical in appearance, and there were 8 nucleated red blood cells per 100 white cells.
A bone marrow sample, obtained by aspiration from the sternum, was hypocellular with marked erythroid hyperplasia and an erythrocyte:granulocyte ratio of 1:1. Although granulocytic maturation was evident, a marked increase in “blast” forms was noted. No previous marrow specimen was available for comparison. Blood cultures yielded no growth.

She was discharged without therapy to the hematology outpatient clinic.

The patient reentered the hospital in May 1962, again because of gingival bleeding and dental abscesses. Except for the presence of fever, the physical findings were as previously described. The white cell count was 17,800/cu. mm. with 28 per cent “blast” cells, 29 per cent neutrophiles and 16 nucleated red cells per 100 white cells. For the first time during the course of the disease platelets were decreased to 46,000/cu. mm. The bleeding time was 15 minutes, the clotting time was 7 minutes and clot retraction was good in 2 hours. The leucocyte alkaline phosphatase was markedly decreased and only a few peroxidase positive granules were noted in the white cells.

Therapy with penicillin was instituted immediately. On the fourth hospital day, infusions of platelet rich plasma were given and additional dental extractions performed.

Despite initial improvement, the patient’s condition gradually deteriorated. Fever was persistent and both the liver and the spleen became palpable. As anemia developed, the white cell count rose to levels of 115,000/cu. mm. Nucleated red cells were prominent on the stained peripheral blood film. Many of these cells were bizarre in their morphologic appearance and the nuclear chromatin pattern frequently resembled that of megaloblastic erythroblasts. The percentage of “blast” cells also increased and micromyeloblasts were noted.

A diagnosis of acute myeloblastic leukemia was made. Therapy was instituted initially with 6-Mercaptopurine 250 mg. daily and, later, with Methylglyoxal-bis-guanylhydrazone (methyl CAG). Although a decrease in the total circulating leucocytes was noted there was no improvement in the patient’s clinical state.

Laboratory studies revealed the following: serum bilirubin 4.4 mg. per cent SCOT 150 units per ml., blood urea nitrogen 125 mg. per cent and uric acid 17.6 mg. per cent Stool specimens were positive for blood.

Transfusions of 250 ml. of packed red cells were given without reactions on two separate occasions. During the third transfusion, respirations suddenly ceased and the patient expired.

No autopsy was performed.

**DISCUSSION**

The syndrome of PNH is characterized by the presence of anemia and by the occurrence of gross hemoglobinuria, evident chiefly in morning urine specimen. The hemolysis may be rapid and severe, resulting in the appearance of fever, jaundice and lumbar pain.

In addition to the anemia, peripheral blood findings usually include reticulocytosis, leukopenia, variable degrees of thrombocytopenia, hapto-globinemia, and hemoglobinemia or methemalbuminemia. Although hemoglobinuria occurs episodically, hemosiderin is regularly detectable in the urine.

The erythrocyte defect considered specific for PNH can be detected by the acidified-serum test. Under standardized conditions affected red cells undergo abnormal lysis when incubated in the patient’s own serum or in serum obtained from a normal person. Such lysis does not occur when either serum sample is inactivated by heating. The absence of abnormal lysis of normal red cells, when incubated in the patient’s acidified serum, confirms the impression that the defect is primarily erythrocytic and not immunologic in origin.

By the aforementioned criteria, the patient described in this report had
PNH. Prior to the development of leukemia, she had manifested an increased susceptibility to infection. It is of interest that a qualitative defect in leucocytes has been described, and that the susceptibility to infection has been related to a functional abnormality in the white cells.

The development of acute myeloblastic leukemia in this patient with PNH was a surprising event. However, in view of the bone marrow hypoplasia which has previously been reported to occur in PNH (with or without associated drug toxicity) the occurrence of acute leukemia as a terminal event may not have been coincidental.

**SUMMARY**

In a case of paroxysmal nocturnal hemoglobinuria, documented since 1955, the features of acute leukemia became evident in 1962, leading to quick death. Between 1960 and 1962, indications of PNH became greatly diminished and a slight, nonspecific leukocytosis developed. No apparent etiologic agent either for the PNH or the acute leukemia could be elicited.

**SUMMARIO IN INTERLINGUA**

In un caso de paroxysmic hemoglobinuria nocturne, documentate depost 1955, le caracteristicas de leucemia acute deveniva evident en 1962, resultante rapidemente in le morte del subjecto. Inter 1960 e 1962, le evidentia de paroxysmic hemoglobinuria nocturne deveniva grandemente reducite, e un leve grado de leucocytosis nonspecific se disveloppava. Nulle apparente agente etiologic poteva esser identificate pro le paroxysmic hemoglobinuria nocturne e nulle pro le leucemia acute.

**REFERENCES**

Paroxysmal Nocturnal Hemoglobinuria with Acute Leukemia

DOROTHY HOLDEN and HERBERT LICHTMAN