Paroxysmal Nocturnal Hemoglobinuria Terminating in Acute Granulocytic Leukemia

By RETO W. KAUFMANN, GERALDINE P. SCHECHTER AND WILLIAM MCFARLAND

Paroxysmal nocturnal hemoglobinuria (PNH) is a serious hemolytic disease characterized by intravascular hemolysis due to an intrinsic defect in the erythrocyte.1,2 The fact that the defect is acquired is of particular significance, yet attempts to define it in metabolic or physiologic terms have thus far been unsuccessful. From an etiologic standpoint, Dacie called attention to the not uncommon association of hypoplastic anemia with PNH and suggested that the two conditions may be causally related.3 Dameshek extended the concept to include certain cases of leukemia in the interrelationship.4

The patient who is the subject of this report is particularly pertinent in that he had both PNH and acute granulocytic leukemia. Early in his illness he exhibited predominantly the manifestations of PNH but he died three years later of acute leukemia.

Case Summary

The patient N. B., a 58 year old Negro male, was admitted to the Veterans Administration Hospital of Washington, D. C. in 1964 for evaluation of a chronic anemia and the recent appearance of immature cells in the blood. Previously he had been hospitalized elsewhere between 1959 and 1961 for eighteen months with active pulmonary tuberculosis. Therapy consisted of Isoniazid (INH) and P-aminosalicylic acid (PAS), and response was satisfactory. No hematologic abnormalities were noted during this hospitalization. INH and PAS were continued on an out patient basis over the next three years.

The patient was noted to be anemic for the first time in 1962 in the course of follow-up clinic visits for tuberculosis. Between 1962 and 1964 the hematocrit ranged between 25 per cent and 34 per cent and on several occasions nucleated red blood cells were seen on the peripheral blood smears. A complaint of dark urine led to a urological examination which disclosed no abnormalities. During this period the patient received vitamin C, injections of vitamin B12 and iron therapy without any improvement in the anemia. In April of 1964 the laboratory reported myeloblasts to be present in the peripheral blood, and the patient was hospitalized.

At that time the patient had no specific complaints referable to his anemia, but on direct questioning he did recall a number of episodes of dark urine. There were no pertinent abnormal physical findings.

The hematocrit was 27 per cent with 9.5 per cent reticulocytes. The red blood cells showed moderate aniso-and poikilocytosis, and occasional nucleated red cells were visible. The white blood cell count was 4000/mm³ with 31 per cent neutrophils, 25 per cent bands, 2 per cent metamyelocytes, 4 per cent myeloblasts, 24 per cent

From Veterans Administration Hospital and Georgetown University School of Medicine, Washington, D. C.

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RETO W. KAUFMANN, M.D.: Fellow in Hematology, VA Hospital, Washington, D.C.
GERALDINE P. SCHECHTER, M.D.: Research Associate in Hematology, VA Hospital, Washington, D.C.
WILLIAM MCFARLAND, M.D.: Chief, Hematology Research Section, VA Hospital and Associate Professor of Medicine, Georgetown University, Washington, D.C.

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lymphocytes and 13 per cent monocytes. The platelet count was 274,000/mm³. Bone
marrow aspiration yielded an inadequate specimen on two occasions. Needle biopsy
showed a marked decrease in fat spaces and areas of fibrosis interspersed with islands
of erythroid hyperplasia. The granulocytic elements did not appear abnormal.

The plasma hemoglobin was 124 mg. per cent and serum haptoglobin was absent.
The total serum bilirubin was 1.5 mg. per cent, with 0.8 mg. per cent direct-reacting
fraction. The Coombs’ test was negative and red cell glucose-6-phosphate dehydrogenase
was normal. Hemoglobin electrophoresis demonstrated A hemoglobin. The urine contained
free hemoglobin and abundant hemosiderin. Iron determination of a 24 hour urine
specimen was 9.4 mg./L. The serum iron was 165 μg. per cent. The clinical suspicion
of paroxysmal nocturnal hemoglobinuria was confirmed by both positive acid hemolysis
and thrombin hemolysis tests. There was no detectable leukocyte alkaline phosphatase
activity.

The course of the patient’s illness is charted in Figure 1. Therapy during the next
three years following the diagnosis of PNH consisted mainly of transfusions of packed
cells, oral iron, and androgens. INH and PAS were discontinued. By 1964 the patient had
received five years of antituberculous therapy, and chest x-ray had shown no change in
the preceding three years.

In late 1964 he was readmitted with a severe episode of hemolysis with hemoglobinuria
and hemoglobinemia. In 1965 hospitalization was again required on three
separate occasions for transfusions when the hematocrit fell below 20 per cent. Moderate
congestive heart failure developed for which the patient received digitalis. Except for
these episodes of acute hemolysis, the hematocrit usually ranged between 20 and 30
per cent, with reticulocytes of 6 to 14 per cent, and white blood counts between 2000
and 4500 with 1 to 6 per cent myeloblasts.

In January 1966 the patient sustained an episode of thrombophlebitis and presumptive
pulmonary infarction. The percentage of myeloblasts in the peripheral blood
was 13 per cent at that time. In March 1966 they were noted to be as high as 23 per
cent. Thrombocytopenia (48,000 platelets/mm³) and reticulocytopenia were noted in
July 1966 and it was evident that his transfusion requirement was increasing. He
complained of crampy abdominal pain and was found to have guaiac-positive stools.
X-ray examination of the gastrointestinal tract on two occasions was negative. On the basis that a right inguinal hernia might be contributing to the patient’s difficulty, a herniorrhaphy was performed in August 1966. The postoperative course was marked by bleeding at the wound site and increased hemolysis.

In November 1966, two weeks following discharge from the surgical service, the patient again returned with severe anemia. The hematocrit was 12 per cent, the white blood count 5100 with 18 per cent myeloblasts, and the platelet count was 54,000. Bone marrow aspiration again yielded a “dry tap.” Needle biopsy showed mostly myeloblasts with some red cell precursors, some fibrosis and markedly decreased fat. It was concluded that there was sufficient evidence for acute leukemia to warrant therapy for it. Over the next six months he received prednisone, 6-mercaptopurine, vincristine and cytoxan sequentially and in combination with little beneficial effect. The anemia and thrombocytopenia persisted and worsened and the myeloblast percentage increased to a level of 70 per cent just before death. An unrelenting problem was the development of a large abscess at the bone marrow biopsy site which was refractory to antibiotics and surgical drainage. The patient expired in April 1967 of a gastrointestinal hemorrhage, five years after the onset of the hemolytic anemia, and three years after myeloblasts were first noted in the blood.

Relevant postmortem findings included a moderate amount of blood in the stomach with hyperemia of the gastric mucosa but no obvious ulceration or localized bleeding site. There was minimal leukemic infiltration of the lungs, liver, spleen and lymph nodes without evidence of myeloid metaplasia. The bone marrow was generally hypocellular with areas of immature myeloid hyperplasia. Fibrosis was not present in the areas examined. There was a marked excess of hemosiderin in the convoluted tubules and interstitial macrophages of the kidneys.

**DISCUSSION**

This patient satisfied all of the diagnostic criteria for PNH. For two years there had been a persistent anemia, and the patient had noticed dark urine on a number of occasions. Thrombophlebitis, a common complication of PNH, developed with pulmonary embolization. Tests for hemosiderinuria, acid hemolysis and thrombin hemolysis were all positive. Throughout his disease repeated examinations for hemosiderinuria, and a “sugar-water test” late in the course of his illness, were positive.

The point at which he developed acute leukemia is difficult to establish. During clinic visits from 1962 to 1964 a number of blood counts were done because of the persistent anemia, and there was no mention of immature myeloid cells. The same laboratory reported myeloblasts for the first time in March, 1964, thus prompting his admission. Immature granulocytic elements in the blood, including myeloblasts, were confirmed when the patient was first examined. Although this finding is held to be highly unlikely in PNH, we were reluctant to attribute it to another process vis à vis strong evidence for PNH.

Bone marrow examination however, added another atypical finding. Marrow aspiration was unsuccessful but needle biopsy showed distinctly abnormal architecture. There were practically no fat spaces. There was a moderate amount of fibrosis surrounding areas of hematopoiesis consisting predominantly of erythroid activity. The usual question arose concerning the significance of the fibrosis. Did this represent myelofibrosis with myeloid metaplasia or merely fibrosis secondary to the PNH? The latter possibility was raised by Dameshek and Fudenberg with regard to another highly unusual patient with
myelofibrosis and myeloid metaplasia who developed paroxysmal nocturnal hemoglobinuria. 9

Since the spleen was not palpable, liver biopsy was performed in an effort to demonstrate myeloid metaplasia. There were no definite islands of hematopoiesis in the liver to support this diagnosis. There were rare nucleated red blood cells found in a few sinusoidal areas, but this was at a time when nucleated red blood cells could be seen on the blood smear. It seemed justified to conclude that a myeloproliferative process was operative, but it could not be categorized further.

In 1966 however, myeloblasts increased rather sharply, thrombocytopenia developed for the first time, and the patient required more frequent transfusions for his anemia. Repeat needle biopsy of the bone marrow at this time showed the same degree of fibrosis as previously, but the normoblastic hyperplasia was replaced with myeloblastic hyperplasia.

The etiologies of these two rare diseases remain unknown and why they should occur in the same individual is even more enigmatic. The possibility that pulmonary tuberculosis or its therapy played an etiologic role in this patient seems remote. Although lymphohematogenous tuberculosis is known to mimic many serious hematologic disorders, our patient had essentially normal blood counts while he had active tuberculosis and during two of the five years he was treated with INH and PAS. Drug therapy of almost any kind must always remain suspect.

The association of aplastic anemia with PNH is now well-recognized. 3 A number of cases have been reported following drug induced hypoplasia. 10 Our patient may have had an hypoplastic process at the onset of his anemia, but it seems unlikely in the absence of leukopenia and thrombocytopenia. In this regard Lewis and Dacie 3 have suggested that the red cell defect leading to PNH may be more likely to arise in a marrow undergoing hematopoietic regeneration following an injury. They envision the proliferation of a damaged or mutated clone which has survived the marrow insult responsible for aplasia. Dameshek 4 has called this cell line a “neoplastic” clone and likens it to the leukemic populations that have been noted to develop following an aplastic phase due to a congenital defect, radiation or chemical injury. In support of this thesis he cited three patients who developed acute myeloblastic leukemia following chloramphenicol-induced aplastic anemia. 11 He suggested that similar processes may be operative in the hypoplastic marrow leading to PNH in one patient and leukemia in another.

This hypothesis would seem to be particularly suited to our patient in the sense that the same factor which produced permanent damage to red cell progenitors eventually affected granulocyte production causing acute granulocytic leukemia. The idea is attractive but the fact that there have not been more reports of the combined defect in the same patient argues against it. We are aware of only one other patient with PNH who developed acute leukemia. 12 Perhaps a more diligent search for the red cell defect characteristic of PNH or “formes frustes” would be fruitful in patients with otherwise “ordinary” granulocytic leukemia.
A 58 year old male who developed paroxysmal nocturnal hemoglobinuria and acute granulocytic leukemia is described. This rare occurrence is pertinent in view of recent concepts suggesting common etiologic mechanisms for these diseases.

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