

NATURAL HISTORY OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Abstract Background. Paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis, is an acquired clonal disorder associated with a somatic mutation in a totipotent hematopoietic stem cell. An understanding of the natural history of PNH is essential to improve therapy.

Methods. We have followed a group of 80 consecutive patients with PNH who were referred to Hammersmith Hospital, London, between 1940 and 1970. They were treated with supportive measures, such as oral anticoagulant therapy after established thromboses, and transfusions.

Results. The median age of the patients at the time of diagnosis was 42 years (range, 16 to 75), and the median survival after diagnosis was 10 years, with 22 patients (28 percent) surviving for 25 years. Sixty patients have died; 28 of the 48 patients for whom the cause of

death is known died from either venous thrombosis or hemorrhage. Thirty-one patients (39 percent) had one or more episodes of venous thrombosis during their illness. Of the 35 patients who survived for 10 years or more, 12 had a spontaneous clinical recovery. No PNH-affected cells were found among the erythrocytes or neutrophils of the patients in prolonged remission, but a few PNH-affected lymphocytes were detectable in three of the four patients tested. Leukemia did not develop in any of the patients.

Conclusions. PNH is a chronic disorder that curtails life. A spontaneous long-term remission can occur, which must be taken into account when considering potentially dangerous treatments, such as bone marrow transplantation. Platelet transfusions should be given, as appropriate, and long-term anticoagulation therapy should be considered for all patients. (N Engl J Med 1995;333:1253-8.)

PAROXYSMAL nocturnal hemoglobinuria (PNH) is an acquired disorder of hematopoiesis characterized by intravascular hemolysis and manifested by episodes of hemoglobinuria and life-threatening venous thromboses.¹ The cellular abnormality in this disorder is caused by a somatic mutation in a totipotent hematopoietic stem cell.^{2,3} The cells derived from the abnormal clone are deficient in all surface proteins normally attached to the cell membrane by a glycosylphosphatidylinositol anchor.^{4,5}

PNH was first described as a distinct clinical entity in 1882.⁶ The cardinal diagnostic test, introduced in the late 1930s, is Ham's test,⁷ which is based on the increased sensitivity of PNH-affected erythrocytes to lysis by complement. Deficiency of an antigen known as the membrane inhibitor of reactive lysis (CD59) is largely responsible for the hemolysis^{8,9} and is implicated in the tendency for patients to have thromboses.⁹ In the past two years the biochemical defect underlying PNH has been pinpointed at an early step in the biosynthesis of glycosylphosphatidylinositol molecules — namely, the transfer of *N*-acetylglucosamine to phosphatidylinositol.¹⁰⁻¹² The protein required for this step is encoded by a gene, *PIG-A*, that is somatically mutated in patients with PNH.¹³⁻¹⁷

Despite the remarkable progress in our understanding of this disorder, treatment has remained largely supportive. The only potentially curative therapy currently available is bone marrow transplantation,^{18,19} which is associated with substantial morbidity and mor-

tality.²⁰ To determine whether the management of PNH can be improved, it is important to know its natural history. We report the results of a long-term study (up to 48 years after the diagnosis) of a group of 80 patients with PNH seen at one institution between 1940 and 1970. This study has uncovered some surprising information on the natural history of the disorder and has identified relatively simple therapies that may reduce the associated morbidity and mortality.

METHODS

Patients

Eighty patients with PNH were referred to Hammersmith Hospital in London between 1940 and 1970. In all patients the diagnosis was established or confirmed by a positive Ham's test.²¹ This group of patients was last described in 1972.²² Follow-up data have been obtained by contacting the patients' primary physicians and reviewing death certificates.

Complications and Causes of Death

The complications and causes of death reported were either unequivocally diagnosable on clinical grounds or were diagnosed after death. If a complication was not confirmed, it is not reported here. Thus, the reported incidence of complications is likely to be an underestimate, because many of the patients were seen at Hammersmith Hospital only infrequently. We compared the survival of the patients with the survival of a control group matched for sex and age.

Analysis of Blood Samples

In 1993 venous blood samples were obtained from five patients in either acid-citrate-dextrose or EDTA for the performance of Ham's tests and flow cytometric studies of the expression of glycosylphosphatidylinositol-linked proteins on erythrocytes and white cells, as previously described.^{23,24} By definition, normal cells express normal levels of glycosylphosphatidylinositol-linked proteins, whereas PNH-affected cells are deficient in all these proteins.

RESULTS

Follow-up Studies

Sixty of the 80 patients were known to have died, and 6 patients were lost to follow-up before 1972. The remaining 14 patients were alive when last seen between

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1975 and 1994, and 9 of the 14 were known to be alive in 1994.

Clinical Presentation

The presenting features or initial diagnoses were reported previously.²² The median age at the time of diagnosis was 42 years (range, 16 to 75). Forty-three (84 percent) of the 51 patients for whom reliable information was available had episodes of hemoglobinuria as a chief symptom at some time during their illness.

Course of Illness and Survival

The course of the disease in each of the 80 patients is shown in Figure 1. From the actuarial survival curve for the group, we calculated a median survival of approximately 10 years (Fig. 2). Twenty-five years after the diagnosis, 58 patients (72 percent) had died, and 22 (28 percent) were alive. The median age at the time of death was 56 years (range, 20 to 84), with a median interval of 10 years (range, 0 to 48) between diagnosis and death. Patient 10 received the diagnosis of PNH in 1939, had a spontaneous remission in 1949, and died of bronchial carcinoma in 1987, 48 years after the diagnosis.

Cause of Death

For 12 of the 60 patients who died (Table 1), the cause of death was unknown. In 28 of the other 48

patients (58 percent), the cause of death (either thrombosis or hemorrhage attributable to thrombocytopenia) was directly related to PNH. In the other 20 patients (42 percent), the cause of death was unrelated to PNH.

Venous Thrombosis

Thirty-one patients (39 percent) were known to have had one or more episodes of venous thrombosis during the course of their illness (Table 2), and several patients had repeated thromboses. In many patients the thrombosis was either fatal or life-threatening, and it was often unheralded.

Spontaneous Remission

Twelve patients (15 percent) had spontaneous clinical remissions (Fig. 1), with negative Ham's tests in all nine who were tested. We later obtained blood samples from five of these nine patients; in all five the erythrocytes expressed normal levels of glycosylphosphatidylinositol-linked proteins, with no demonstrable PNH-affected erythrocytes (Fig. 3A). In addition, of the four patients tested, none had PNH-affected neutrophils (Fig. 3A), but three of the four had small numbers of PNH-affected lymphocytes (Fig. 3B). Further analysis by double fluorescent staining demonstrated a subpopulation of PNH-affected lymphocytes among CD4+

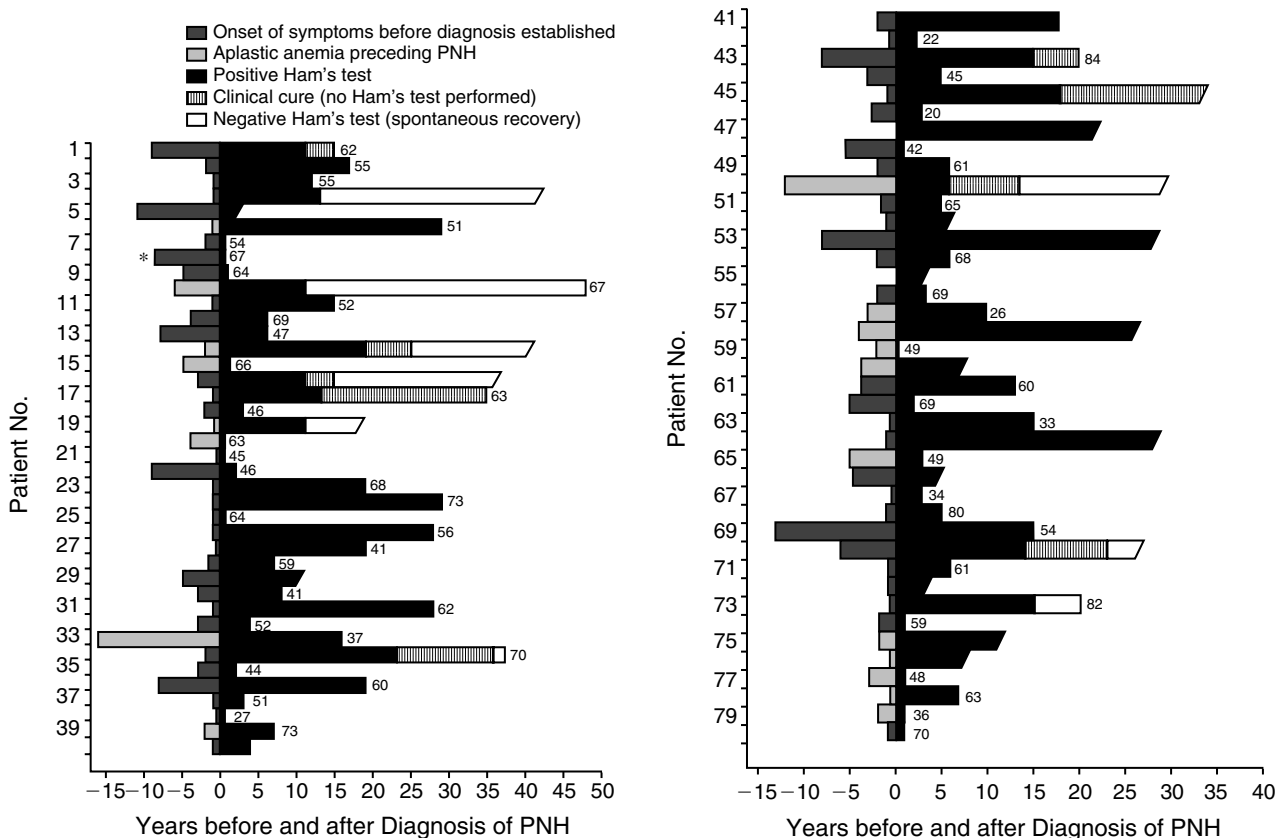


Figure 1. Course of Illness in 80 Consecutive Patients with PNH.

The x axis indicates the years before and after the diagnosis of PNH, which is denoted by the zero on the axis. Bars ending in a straight line indicate patients who died, and their ages at death are shown; bars ending in a diagonal line indicate surviving patients. Nine patients had complete clinical recovery, with negative Ham's tests. Three additional patients had protracted clinical remissions, but Ham's test was not repeated during remission. The asterisk indicates a prolonged but unspecified period of symptoms before the diagnosis was established.

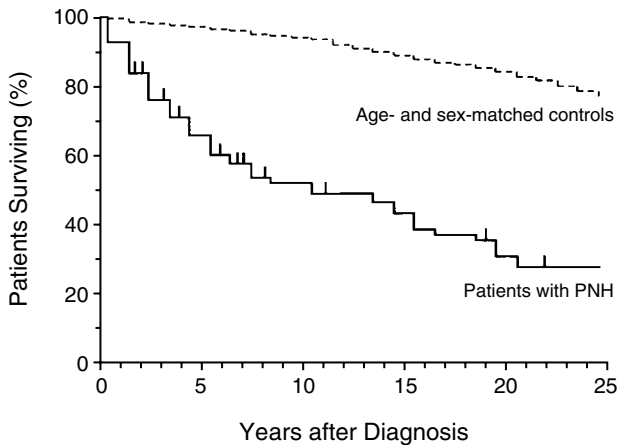


Figure 2. Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH.

The median survival was 10 years. The expected survival of an age- and sex-matched control group is shown for comparison.

T cells, CD8+ T cells, and CD19+ B cells in all three patients.

Associated Disorders

Twenty-three patients (29 percent) received a diagnosis of aplastic anemia before the diagnosis of PNH. Nine of these patients subsequently had hemolytic PNH, with episodes of overt hemoglobinuria, and six did not; whether the remaining eight patients ever had hemoglobinuria could not be reliably determined.

At the time of the diagnosis, 64 of the 80 patients (80 percent) had thrombocytopenia (platelet count, <150,000 per cubic millimeter), and 38 patients (48 percent) had severe thrombocytopenia (platelet count, <50,000 per cubic millimeter). In addition, 44 patients (55 percent) had neutropenia (neutrophil count, <1500 per cubic millimeter).

In five patients the disorder progressed from hemolytic PNH to aplasia. Ham's test remained positive in four of these patients, but the fifth (Patient 34) subsequently had a negative Ham's test, with no PNH-affected erythrocytes or neutrophils. The patient died from bleeding due to severe thrombocytopenia 37 years after the diagnosis of PNH and at least 8 years after Ham's test had become negative.

Leukemia was not known to have developed in any of the patients.

DISCUSSION

Clinical Features

In this group of 80 patients who were followed for up to 48 years, the median actuarial survival was 10 years, with 28 percent of the patients surviving for 25 years. Death was directly attributable to PNH or to bone marrow hypoplasia in 58 percent of the patients who died. Therapy with platelet concentrates should reduce mortality from hemorrhage due to thrombocytopenia.

At least 39 percent of the patients had venous thrombosis at some time during their illness. Many patients had initial thromboses that were life-threatening, but two (Patients 17 and 70), who probably had postpar-

tum hepatic-vein thrombosis, recovered and survived for 34 and 27 years, respectively, after the thrombosis. One other patient (Patient 34) survived for 24 years after a thrombosis of the inferior mesenteric vein.

Spontaneous Remission

In some patients with PNH, the severity of the illness diminishes with time,²⁵ and some patients have a complete clinical remission,^{22,26} although laboratory abnormalities may persist for years.²⁷ In this series 15 percent of the patients had spontaneous clinical remissions, and Ham's test became negative in the patients who were tested. Neither the severity of symptoms or complications nor the proportion of red cells lysed in Ham's test was correlated with an eventual remission. Among the patients with remissions, one (Patient 14) had severe, transfusion-dependent PNH and thromboses, and at

Table 1. Causes of Death in 60 Patients with PNH.

CAUSE OF DEATH	NO. OF PATIENTS
Probably related to PNH	
Venous thrombosis	
Hepatic vein	7
Inferior vena cava	1
Cerebral vein	1
Mesenteric vein	2
Pulmonary embolism	3
Hemorrhage	
Gastrointestinal	6
Subarachnoid	3
Intracerebral	2
Miscellaneous	
Liver failure	2
Intraabdominal event	1
Probably unrelated to PNH	
Arterial thrombosis	
Myocardial infarction	6
Cerebrovascular accident	2
Bronchopneumonia	3
Chronic obstructive airways disease plus cor pulmonale	2
Cardiac tamponade	1
Constrictive pericarditis	1
Renal failure	1
Amyloidosis	1
Lymphoma	1
Bronchial carcinoma	1
Epilepsy	1
Unknown	12

Table 2. Sites and Types of Thrombosis.

SITE AND TYPE OF THROMBOSIS	NO. OF PATIENTS
Intraabdominal	
Hepatic vein	8
Inferior vena cava	3
Mesenteric vein	4
Splenic vein	1
Renal vein	1
Unspecified	1
Other venous sites	
Cerebral vein	4
Pulmonary embolism	9
Deep vein	7
Superficial	3
Arterial	
Myocardial infarction	6
Cerebrovascular accident	2

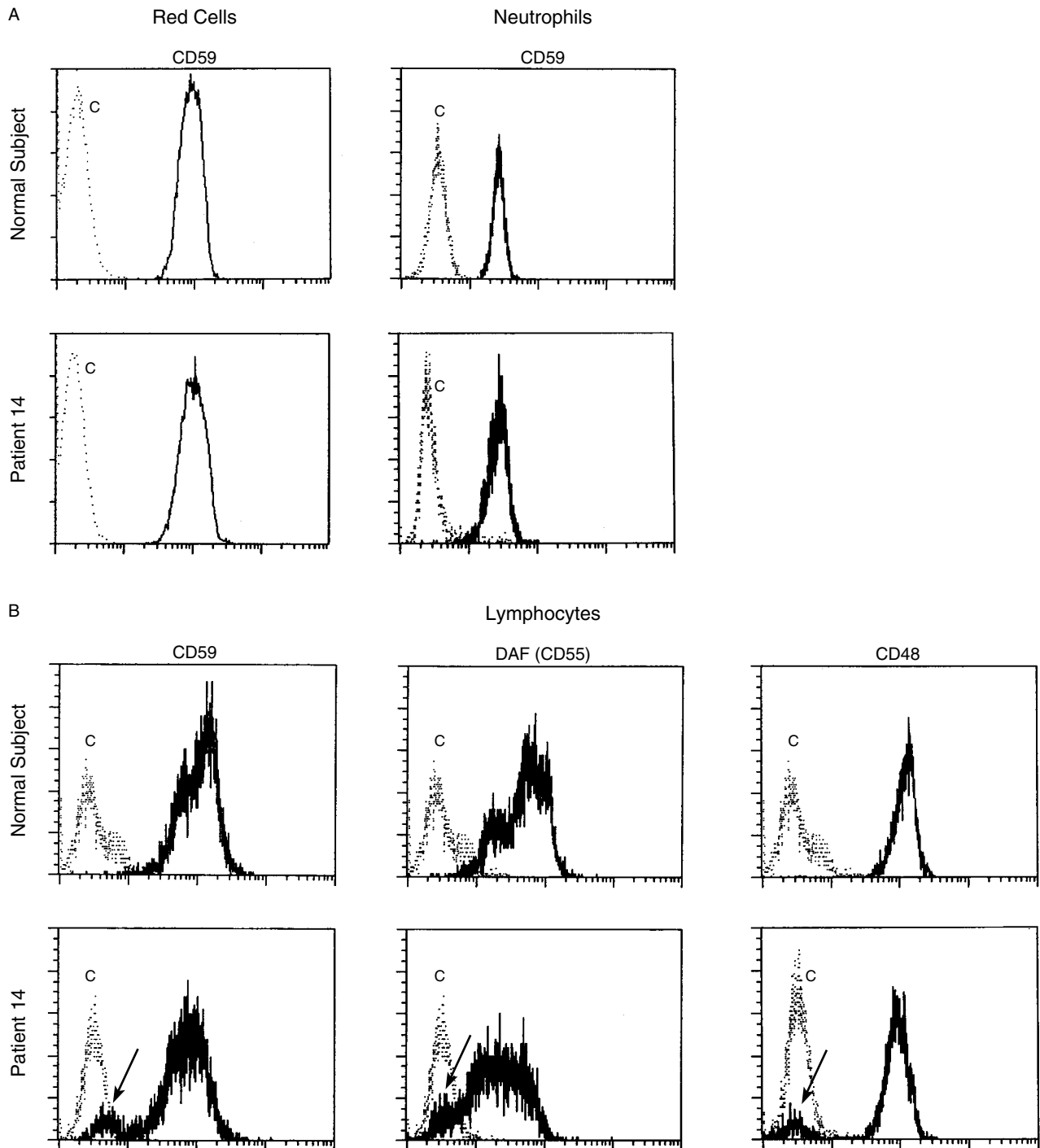


Figure 3. Flow-Cytometric Analysis of Blood Cells from a Normal Subject and Patient 14 after Spontaneous Recovery from PNH. The analysis was carried out 20 years after the patient's clinical remission began and 17 years after her Ham's test had become negative. Panel A shows a unimodal distribution of cells with normal reactivity after reaction with anti-CD59 antibody (a molecule absent from the surface of PNH-affected cells). The distributions obtained with the patient's red cells and neutrophils are indistinguishable from those of the cells from a normal subject, demonstrating that no PNH-affected cells remain. C indicates distributions obtained in control experiments with an antibody directed against a molecule absent from normal blood cells.

Panel B shows the results of an analysis, similar to that in Panel A, carried out on peripheral-blood lymphocytes. The distributions of cells from a normal subject show that, as compared with the results of analyses with negative control antibody (C), all the lymphocytes reacted with all three antibodies used. The distribution is unimodal for CD48 and bimodal for CD59 and CD55. In contrast, the cells from Patient 14 have a small population of lymphocytes that are unreactive with all three antibodies (arrows), which indicates that these cells lack the corresponding antigen protein molecules on their surfaces. The fact that there is a peak of antigen-negative cells for three different proteins that are normally attached to the cell membrane by a glycosylphosphatidylinositol anchor means that the anchor is absent, which is characteristic of the PNH phenotype. The finding that the PNH clone was still present when there were no PNH-affected erythroid or myeloid cells in Patient 14 during a clinical and hematologic remission is consistent with the notion that this clone does not have a selective advantage once normal hematopoiesis has resumed. DAF denotes decay-accelerating factor.

least two had over 50 percent lysis in earlier Ham's tests, suggesting that they had few residual normal stem cells at the height of their illness. The spontaneous remissions occurred between 10 and 20 years after the diagnosis of PNH. Of the 35 patients who survived 10 years or more, 12 (34 percent) eventually had remissions. A possible explanation for spontaneous remission is that the clones of PNH-affected cells have a finite life span, like normal somatic cells. Recovery may thus depend on the presence of normal stem cells capable of repopulating the bone marrow.²⁸

There were no erythrocytes or neutrophils affected by PNH after recovery, but three of four patients tested had some residual abnormal lymphocytes. These results are consistent with the fact that lymphocytes have a much longer life span than myeloid and erythroid cells and that committed lymphocyte progenitor cells undergo division less frequently than the other cells. If the aging process postulated as being responsible for the gradual disappearance of clones of PNH-affected cells is related to the number of cell divisions, this may explain why abnormal lymphocytes persist for many years after the disappearance of abnormal neutrophils and erythrocytes.

PNH and Bone Marrow Failure

The data on this series of patients provide further evidence of the close relation between PNH and aplastic anemia. The coexistence of the two conditions in one patient was first reported in 1944,²⁹ with subsequent reports in 1952³⁰ and 1961.³¹ Cultures of peripheral blood and bone marrow from patients with PNH consistently show reduced numbers of erythroid progenitor cells (erythroid burst-forming units) and myeloid progenitor cells (granulocyte-macrophage colony-forming units), even in the absence of pancytopenia,^{32,33} as in patients with aplastic anemia.³⁴ In addition, PNH eventually develops in 10 to 31 percent of patients with aplastic anemia treated with immunosuppressive agents.³⁵ It is important to emphasize that PNH is not a complication of immunosuppressive treatment. Instead, the majority of patients with this disorder probably have an underlying aplastic process. Clones of PNH-affected cells may thus have a relative growth or survival advantage over the residual normal bone marrow in patients who have aplastic anemia.^{1,28,36} It is conceivable that the mutation leading to the development of PNH occurs quite frequently but that, in the absence of marrow hypoplasia, the clone has difficulty establishing itself.²⁸

PNH and Leukemia

Because of the reports of myelodysplasia and leukemia¹ — invariably, acute myeloid leukemia — in patients with PNH, it has been regarded as a preleukemic condition. Leukemia did not develop in any of our 80 patients, however, indicating that it is relatively rare in unselected patients with PNH. Acute myeloid leukemia eventually develops in approximately 5 percent of patients with aplastic anemia who survive the marrow aplasia.³⁵ Thus, aplastic anemia may predispose patients to both PNH and acute myeloid leukemia, but the

development of PNH may not add to the risk of leukemia associated with uncomplicated aplastic anemia.

In most reported cases of leukemia in patients with PNH in whom the leukemic cells were studied,^{37,38} the leukemic clone was derived from the PNH clone. According to a recent report of a patient with PNH who subsequently had a myelodysplastic syndrome, the blasts expressed normal levels of glycosylphosphatidylinositol-linked proteins,³⁹ indicating that the leukemic event may occur in the residual normal stem cells.

Management

The natural history of PNH is an important factor in decisions about therapy for individual patients. Thrombolytic treatment of hepatic-vein thrombosis with tissue plasminogen activator has been reported to be effective.⁴⁰ Oral anticoagulation therapy after venous thrombosis has been used since the 1950s.²⁵ In view of the high incidence of potentially fatal thrombosis, a strong case can be made for prophylactic anticoagulation treatment in all patients with PNH in whom there is no contraindication (such as severe thrombocytopenia). This approach may improve survival and reduce morbidity.

The only curative therapy at present is bone marrow transplantation, but it is available to only a small proportion of patients and is associated with substantial morbidity and mortality. The recent advances in the understanding of the pathogenesis of PNH and, in particular, of the molecular lesion open opportunities to explore new treatments, such as gene therapy. The possibility of spontaneous remission and of long-term survival must be taken into account when considering either bone marrow transplantation or other new treatments for this disorder.

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