Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare but potentially fatal hematopoietic stem cell disease caused by a mutation in the PIG-A gene that confers sensitivity to complement-mediated lysis to all blood cell lineages. Aplastic anemia is closely related to PNH, and approximately 20% of patients with aplastic anemia have concurrent PNH at diagnosis. The relationship between PNH and aplastic anemia has been proposed to arise from partially overlapping etiologies. It is important to test for PNH in patients with aplastic anemia, not only to establish the presence of PNH clones, but also because the presence of PNH cells is associated with a superior response to immunotherapy. Early diagnosis of PNH by flow cytometry of peripheral blood is essential for improving the patient’s prognosis. Other tests to establish a diagnosis of PNH include a complete blood cell count, reticulocyte count, serum concentration of lactate dehydrogenase, fractionated bilirubin, and haptoglobin, as well as bone marrow assessment and cytogenetic analysis. PNH symptoms are associated with hemolytic anemia, bone marrow failure, and thrombosis, whereas those of aplastic anemia arise from cytopenia. Because PNH involves clonal expansion of mutated cells, the early phase of the disease involves few or no symptoms. As the clonal population expands, many patients will experience symptoms such as fatigue, headache, abdominal pain, and episodes of dark urine.
Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired stem cell disorder characterized by clonal expansion of blood cells that are highly susceptible to complement-mediated lysis. Although the exact incidence of PNH is not known, a British study found an annual incidence of 0.13 cases per 100,000 inhabitants and an estimated 15-year prevalence of 1.59 per 100,000. PNH is a hemolytic anemia. The clonal expansion occurs in mutated hematopoietic stem cells that are prone to complement-mediated lysis. PNH cells have an acquired mutation of the phosphatidylinositol glycan class A (PIG-A) gene that leads to reduced expression or complete loss of the glycosylphosphatidylinositol (GPI) anchor (Figure 1). In normal cells, the GPI anchor tethers proteins such as CD59 (membrane inhibitor of reactive lysis [MIRL]) and CD55 (decay-accelerating factor [DAF]) to the cell surface, protecting the cells against complement-mediated lysis. Cells harboring the PIG-A mutation lack CD59 and CD55 and are thus extremely susceptible to lysis in the presence of activated complement. Because the PIG-A mutation occurs in a stem cell, PNH phenotype cells arise in the red blood cells, platelets, and white blood cells, including granulocytes and monocytes. Although PNH clones initially represent a miniscule proportion of blood cells, the clones can expand and eventually overtake normal cells. The clinical features of PNH result from high levels of complement-mediated lysis of PNH clones as well as the intravascular release of hemoglobin. The latter is associated with kidney dysfunction and depletion of nitric oxide, which plays a role in smooth muscle function. PNH is broadly characterized by hemolytic anemia, thrombosis, and bone marrow hypocellularity. Patient symptoms may include fatigue, shortness of breath, bruising or bleeding, headaches, chest or abdominal pain, pulmonary hypertension, erectile dysfunction, and bouts of dark urine.

Aplastic anemia arises from bone marrow failure that encompasses all 3 blood cell lineages, leading to peripheral pancytopenia and marrow hypoplasia. Based on a prospective, multicenter study conducted between 1980 and 2003 in Barcelona, aplastic anemia is observed in approximately 2.34 out of every 1 million people. Aplastic anemia can be seen in very young patients owing

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to inherited factors. The disease presents most commonly in people between the ages of 15 and 25 years, with a second, smaller peak of incidence after 60 years of age. In older patients, aplastic anemia tends to be associated with more severe symptoms. A study of adult patients with aplastic anemia demonstrated 6-year survival rates of 69% for the 229 patients treated with immunosuppressive therapy and 79% for the 64 patients who received a bone marrow transplant.

Aplastic anemia is closely related to PNH, and approximately 20% of patients with aplastic anemia have concurrent PNH at diagnosis. The relationship between PNH and aplastic anemia has been proposed to arise from partially overlapping etiologies. Aplastic anemia arises from a T-cell–mediated autoimmune attack against hematopoietic stem cells. The attack may be directed specifically at the GPI anchor, as well as other molecules. PNH arises from the same autoimmunity in combination with the PIG-A mutation, whereas the PIG-A mutation alone leads to subclinical effects.

Because of the underlying autoimmunity, immunosuppressive therapy is effective for treatment of both conditions. It is important to test for PNH in patients with aplastic anemia, not only to establish the presence of PNH clones, but also because the presence of PNH cells is associated with a superior response to immunotherapy. In a study of 122 patients with aplastic anemia who received immunosuppressive therapy within 1 year of diagnosis, response rates at 1 year were 91% for those with PNH cells vs 48% for those without PNH cells, and the rate of CRs at 5 years was 36% vs 3%, respectively (Figure 2). In the 83 patients (68%) with PNH cells, defined as CD55-negative/CD59-negative, the proportion of PNH cells ranged from 0.005% to 23.1%. A multivariate analysis showed that the presence of PNH-type granulocytes was the only factor significantly associated with a favorable response to immunosuppressive therapy (P<.001). The presence of PNH cells in aplastic anemia patients is also associated with a better prognosis.

For aplastic anemia patients with PNH clones at subclinical levels (≤5% of granulocytes), it is important to monitor levels of PNH cells every 6 months to provide early evidence of clonal expansion. Expansion of the PNH clone may be accompanied by intravascular hemolysis. Persistent intravascular hemolysis causes anemia, hemoglobinuria, and other complications. Breakdown of the red blood cells commonly occurs during the night, with ongoing concentration of the urine leading to dark, cola-colored urine in the morning.

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Figure 2. In a study of patients with aplastic anemia who received immunosuppressive therapy within 1 year of diagnosis, response rates at 1 year were 91% for those with PNH cells vs 48% for those without PNH cells, and the rate of complete responses at 5 years was 36% vs 3%, respectively. PNH, paroxysmal nocturnal hemoglobinuria. Adapted from Sugimori C et al. Blood. 2006;107(4):1308-1314.
Although aplastic anemia and PNH are related and often occur in the same patient, the 2 diseases show some distinct symptoms. An early diagnosis of PNH is essential to allow initiation of appropriate treatment as soon as possible to address the underlying hemolysis and thus improve the prognosis. In patients with aplastic anemia, symptoms relate to cytopenias and include pallor, shortness of breath, fatigue, and potential bruising owing to the low levels of platelets. Patients are at risk of infection owing to low levels of white blood cells. Infection, mouth sores, or an illness that does not improve may prompt a visit to the doctor’s office and subsequent diagnosis of aplastic anemia. Patients with PNH may also be affected by fatigue, due to hemolysis and attendant anemia, as well as iron deficiency that can develop over time. Thrombosis is also a common presenting feature of PNH, with approximately 90% of cases being venous and the remainder arterial. Thrombosis may cause various symptoms depending on the location, and may include pain and/or swelling of the lower extremities, vision loss, headache, nausea, vomiting, abdominal pain and swelling, and pulmonary hypertension. PNH testing should be performed in patients who present with thrombosis and concomitant cytopenias. Although hemolysis is chronic and ongoing, it may appear to be paroxysmal. Approximately 30% to 40% of cases will manifest with overt hemoglobinuria, which is quite alarming to the patient. Patients may have symptoms related to depletion of nitric oxide, such as abdominal pain or esophageal spasm. Men may experience erectile dysfunction. A small proportion of patients develop chronic kidney disease.

In addition to a history of aplastic anemia, risk factors that point to possible PNH include unexplained symptoms such as thrombosis, evidence of intravascular hemolysis with a negative antiglobulin (Coombs) test, elevated lactate dehydrogenase (LDH), or iron deficiency, particularly with accompanying cytopenias. To diagnose PNH, it is important to obtain a complete blood count and to observe any elevation in the mean corpuscular volume. Patients with recent onset of intravascular hemolysis often present with an elevated reticulocyte count. However, the reticulocyte count may be low if the patient is iron-deficient or if there is concomitant aplastic anemia or myelodysplastic syndrome. In patients with hemolysis, a blood smear is useful to check for spherocytosis, which could be hereditary or caused by an autoimmune process. Iron stores should be evaluated. A negative Coombs test almost completely eliminates the possibility of an autoimmune hemolytic
anemia, making PNH more likely. It is also important to look for evidence of intravascular hemolysis, which is indicated by low levels of haptoglobin. LDH is a measure of hemolysis and thus will be elevated, especially in the presence of active hemolytic anemia. Levels of bilirubin, particularly unconjugated bilirubin, are typically elevated, and hemosiderin may be present in the urine. To confirm a suspected diagnosis of PNH, the gold standard test is flow cytometry of the peripheral blood that evaluates the PNH phenotype on at least 2 types of cells (Figure 3). Most centers look for the PNH phenotype in neutrophils, monocytes, and erythrocytes. For red blood cells, antibodies are used to detect cells lacking CD55 and CD59 on the cell surface. The proportion of PNH cells should be similar in neutrophils and monocytes. However, because PNH red cells are continuously undergoing some degree of hemolysis, the proportion of PNH red cells should be lower. The fluorescein-labeled proaerolysin (FLAER) test detects GPI-deficient neutrophils and monocytes through an inactive variant of aerolysin, which binds selectively to the GPI protein. FLAER, fluorescein-labeled proaerolysin; GPI, glycosylphosphatidylinositol. Adapted from Brodsky RA et al. Am J Clin Pathol. 2000;114(3):459-466.

Figure 4. The FLAER test detects GPI-deficient neutrophils and monocytes through an inactive variant of aerolysin, which binds selectively to the GPI protein. FLAER, fluorescein-labeled proaerolysin; GPI, glycosylphosphatidylinositol. Adapted from Brodsky RA et al. Am J Clin Pathol. 2000;114(3):459-466.

clinical characteristics suggesting the diagnosis of PNH. In these cases, the test should be repeated.

Since patients may have comitant aplastic anemia, it is important to perform a bone marrow aspirate and biopsy. In patients with classic hemolytic PNH, the bone marrow is likely to be hypercellular with a predominance of red cell components. This erythroid hyperplasia occurs to compensate for the hemolysis. If dysplasia is present, it is generally observed in different cell types, and myelodysplasia should be suspected only if the dysplastic features affect more than 1 cell lineage in the bone marrow. In contrast, in patients with aplastic anemia, the bone marrow cells appear normal morphologically, but few cells are present. If aplastic anemia is suspected, chromosomal analyses are needed. It is necessary to ascertain the underlying cause, which can include prior viral infection, including HIV; or a deficiency in copper or another nutrient. Genetic tests, including next-generation sequencing, can uncover hereditary marrow failure syndromes. Although the literature suggests that patients with hereditary marrow failure syndromes generally do not have a PNH clone, next-generation sequencing studies are available and can be used to test the bone marrow for multiple genes related to hereditary marrow failure syndromes. This testing is important, especially if an allogeneic stem cell transplant is being considered because knowledge of the presence of a hereditary marrow failure syndrome will have implications on the choice of donor and conditioning regimen. If myelodysplastic syndrome is suspected, chromosome testing, such as fluorescence in situ hybridization, should be performed. These tests are important in the diagnosis as well as for planning the optimal therapeutic approach for the patient.

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The Role of the Hematopathologist in Diagnosing and Monitoring Paroxysmal Nocturnal Hemoglobinuria and Aplastic Anemia

M. Atef Shrit, MD
Department of Pathology
Miami Valley Hospital
Clinical Associate Professor of Pathology
Wright State University
Boonshoft School of Medicine
Dayton, Ohio

One cannot overemphasize the significance of an early, definitive diagnosis in patients at high risk for PNH. In patients with suspected PNH, high-sensitivity flow cytometry can detect as few as 0.01% of cells with the characteristic GPI-anchor deficit (Figure 5).1 Guidelines for the diagnosis and monitoring of PNH and related disorders by flow cytometry were published in 2010.2 The guidelines cover who should be tested, how testing should be performed, and how results should be reported (Figure 6). PNH is a clinically heterogeneous disease. Patients may present with intravascular hemolysis. Those with mild or absent hemolysis are likely to have unexplained thrombosis or bone marrow dysfunction, manifesting as aplastic anemia or low-risk myelodysplastic syndrome.

The initial evaluation of patients with suspected PNH should include a white blood cell count, reticulocyte count, and a peripheral blood smear. Testing should examine levels of LDH, indirect bilirubin and haptoglobin, direct antiglobulin via the Coombs test, serum ferritin, and iron levels, as well as assess bone marrow and cytogenetics. Testing for PNH with high-sensitivity flow cytometry should be performed on peripheral blood. Samples should be collected in an ethylenediaminetetraacetic acid (EDTA) tube and processed within 24 hours, and at least 250,000 events of each specific cell type must be collected. Analysis should include granulocytes plus red blood cells and/or monocytes. It is important to ensure that more than 1 reagent against the GPI-anchor protein is used to confirm the absence of CD55 and CD59. FLAER has emerged as one of the best reagents to study GPI-linked antigens on granulocytes, since it binds specifically to GPI anchors. Testing is also necessary to determine whether the PNH clone is type II or III.2 PNH type I cells have normal levels of the GPI-anchored proteins CD55 and CD59. PNH type II cells have a partial deficit of CD55 and CD59 and are 2 to 4 times more sensitive to complement, whereas type III cells lack CD55 and CD59 on the cell surface and are 15 to 25 times more sensitive to complement compared with normal cells. If a PNH clone is detected, it is advisable to repeat testing every 6 months for 2 years, and annually thereafter if the clone is stable.

Diagnostic testing will allow patients to be classified into 3 categories based on the recommendation of the International PNH Interest Group.2 Patients with classic PNH have clinical evidence of intravascular hemolysis but no evidence of another defined bone marrow abnormality. These patients have at least 50% PNH granulocytes. The bone marrow in these patients has cells with erythroid hyperplasia and a morphology that is normal or close to normal. Another group consists of patients with PNH in the setting of aplastic anemia, low-risk myelodysplastic syndrome, or another bone marrow disorder. The diagnosis is supported by the presence of nonrandom karyotype abnormalities associated with a specific bone marrow abnormality. Patients in this group show variable proportions of PNH granulocytes; clone levels are 50% or higher in approximately 10% of patients. The third group of patients consists of those with subclinical PNH, based on the presence of small populations (<10%) of hematopoietic cells lacking GPI-anchor proteins.
PNH diagnostic reports should clearly state whether a clone has been identified, and, if applicable, whether the clone size has changed in comparison to any prior testing. Clone size should be noted for each cell lineage, including granulocytes, monocytes, and red blood cells. Finally, it is imperative that hematopathologists provide clear, accurate and timely test results, and collaborate with treating physicians to ensure that patients with the PNH clone are managed appropriately.

**Figure 5.** In patients with suspected PNH, high-sensitivity flow cytometry can detect as few as 0.01% of cells with the characteristic GPI-anchor deficit. GPI-AP, glycosyl phosphatidylinositol (GPI)-anchored proteins; PNH, paroxysmal nocturnal hemoglobinuria. Adapted from Parker C et al. *Blood*. 2005;106(12):3699-3709.

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References
**Case 1: Rapid Expansion of the PNH Clone in a Young Woman With Aplastic Anemia**

M. Atef Shrit, MD  
Department of Pathology  
Miami Valley Hospital  
Clinical Associate Professor of Pathology  
Wright State University  
Boonshoft School of Medicine  
Dayton, Ohio

The patient was a 25-year-old woman who presented with a white blood count of 4.2 \( \times 10^9/L \), platelets at 70,000/\( \mu L \), and a hemoglobin level at 8.4 g/dL. Her absolute neutrophil count was 1.5/\( \mu L \). Bone marrow examination showed normocellular bone marrow with marked megakaryocytic hypoplasia and moderate erythroid hypoplasia. Granulocytic elements were borderline increased. There was no dyspoiesis. Results from cytogenetic testing were normal. The patient was taking an over-the-counter medication that was not identified. The bone marrow findings raised the possibility of emerging aplastic anemia. Flow cytometry of the peripheral blood showed a PNH clone comprising 4% of the total granulocytic count and 3% of the red blood cell count.

The bone marrow was reexamined a month later, and continued to show megakaryocytic and erythroid hypoplasia. The diagnosis of aplastic anemia was made. At that time, repeat testing for PNH showed that the PNH clone had expanded to 5.75% of granulocytic elements. During the following 2 months, the PNH clone expanded to 9.2% of the total granulocytic count. This case illustrates the potential rapid expansion of the PNH clone in patients with aplastic anemia, and emphasizes the need for periodic measurements of the PNH clone in this setting.

David Dingli, MD, PhD  
An article by Araten and colleagues, published in 2001, evaluated the behavioral clone sizes as a function of time. The study included 36 patients, in whom clone size was measured over a period of 1 to 6 years. The authors found that the PNH clone expanded in 12 patients at a rate of over 5% per year. Dr Shrit’s case illustrates an important point: fairly significant fluctuations in clone size can occur in short time intervals.

**Reference**


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**Case 2: Concurrent Presentation of Aplastic Anemia and PNH**

Bart Lee Scott, MD  
Assistant Professor of Medicine, Division of Oncology  
University of Washington  
Director of Hematology and Hematologic Malignancies  
Seattle Cancer Care Alliance  
Fred Hutchinson Cancer Research Center  
Seattle, Washington

The patient is a 44-year-old woman who presented with weakness, as well as a 4-month history of fatigue and shortness of breath. About 3 months before presentation, she had developed pneumonia, which was treated with azithromycin. She had experienced iron deficiency with 2 prior pregnancies. On evaluation, she was noted to have easy bruising and lightheadedness. Her white blood cell count was 2100/\( \mu L \), her platelet count was 31,000/\( \mu L \), her hemoglobin level was 4.1 g/dL, and her hematocrit was 11.6%. The reticulocyte count was 3.1% and the absolute neutrophil count was 860/\( \mu L \), with a mean corpuscular volume of 135 fl. She received a transfusion with 4 units of packed red blood cells, as well as platelet transfusions and iron supplementation. Workup showed normal levels of vitamin B12, red blood cell folate, and thyroid-stimulating hormone; a ferritin level of 40 ng/mL; and an LDH level of 224 U/L. She had hypocellular bone marrow with 40% cellularity. There were megaloblastoid changes in the erythroid and platelet lineage, and her blast count was less than 1%. Flow cytometry of the bone marrow showed a CD34 count of 0.24%.

One month later, I evaluated the patient for a potential diagnosis of myelodysplastic syndrome. Additional blood work showed that her LDH level was 250 U/L. Her haptoglobin was less than 10 mg/dL. The Coombs test was negative. Peripheral blood was ordered for PNH testing, and this showed a GPI-anchor–deficient population present at 68.2% in the neutrophil lineage. As a result, the patient was diagnosed with concurrent aplastic anemia and PNH.

This case illustrates how aplastic anemia and PNH can present concurrently, and how not all patients with aplastic anemia have a subclinical PNH clone. When you see a patient with combined aplastic anemia and PNH, it is important to decide which to treat first. Thrombosis can be quite severe and is a leading cause of death in PNH.

Another interesting aspect of this case was the initial dysplasia observed in the bone marrow. In PNH
patients, the stress of hemolysis can lead to dyserythropoiesis. Results from marrow tests must be evaluated in the appropriate clinical context. This patient was initially sent to me for myelodysplastic syndrome, but the correct diagnosis turned out to be aplastic anemia with a concurrent PNH clone.

M. Atef Shrit, MD  Hematopathologists commonly see patients with severe hemolysis and associated dyserythropoiesis. This condition is referred to as “stress dyserythropoiesis.”

David Dingli, MD, PhD  This condition is not rare. In these cases, communication between an experienced hematopathologist and physician is especially important. Data from Japan suggest that if there is myelodysplastic syndrome with a small PNH clone, it is unlikely that this will be associated with ring sideroblasts.

**Case 3:** A Patient With Type II and Type III PNH Cells

David Dingli, MD, PhD  A 40-year-old woman developed progressive cytopenia. She had normal blood counts documented several years before her presentation. Her initial evaluation at another institution led to a diagnosis of Evans syndrome, based on her mild anemia and thrombocytopenia. Interestingly, her mean corpuscular volume was 102 fL. She then became significantly more symptomatic, with shortness of breath, dark urine, and fatigue. She had to quit working.

When the patient was seen at our institution, testing for PNH showed that she was positive, with a very high percentage of PNH cells—approximately 85% neutrophils. Interestingly, she had both type II and type III PNH cells, with a PNH type II clone of approximately 40% and a PNH type III clone of 14%. The red cell clone size often underestimates the true size of the disease clone because of the short half-life of the red cells. Testing of the bone marrow by next-generation sequencing did not find any mutations associated with a hereditary marrow failure syndrome. There was no evidence of myelodysplastic syndrome. The patient had relative erythroid hyperplasia, but the granulocytes and megakaryocyte lineages were somewhat suppressed.

David Dingli, MD, PhD  That must be one of the youngest patients ever diagnosed with PNH.

M. Atef Shrit, MD  Yes, certainly in my practice.

**Case 4: Diagnosis of PNH in a Young Patient**

M. Atef Shrit, MD  A 14-year-old African American female presented with massive pulmonary embolus. A comprehensive hypercoagulable panel was negative. Unfractionated heparin was started, with a less than optimal response. The patient developed a recurrent pulmonary embolus 1 week later. At that time, testing for PNH by flow cytometry was performed. It showed a large PNH clone, comprising 85% of the total granulocytic count. The patient demonstrated 100% cellular bone marrow, with marked erythroid hyperplasia and so-called “stress dyserythropoiesis.” This case provides an example of a patient with PNH who presented with signs and symptoms of a hypercoagulable state and heparin resistance.

David Dingli, MD, PhD  That must be one of the youngest patients ever diagnosed with PNH.
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Paroxysmal Nocturnal Hemoglobinuria

- PNH is an acquired stem cell disorder characterized by clonal expansion of blood cells that are highly susceptible to complement-mediated lysis
- PNH is broadly characterized by hemolytic anemia, thrombosis, and bone marrow hypopcellularity
- Symptoms include fatigue, shortness of breath, bruising or bleeding, headaches, chest or abdominal pain, pulmonary hypertension, erectile dysfunction, and bouts of dark urine

Risk Factors That Point to Possible PNH

When unexplained, the following symptoms may suggest the possible diagnosis of PNH:
- Thrombosis
- Evidence of intravascular hemolysis with a negative antiglobulin (Coombs) test
- Elevated lactate dehydrogenase
- Iron deficiency, particularly with accompanying cytopenias

Classification According to the International PNH Interest Group

- Classic PNH. Patients have clinical evidence of intravascular hemolysis and >50% PNH granulocytes. The bone marrow has cells with erythroid hyperplasia and a morphology that is normal or close to normal
- PNH in the setting of aplastic anemia, low-risk MDS, or another bone marrow disorder
- Subclinical PNH. This diagnosis is based on the presence of small populations of hematopoietic cells lacking GPI-anchor proteins

Aplastic Anemia

- Arises from bone marrow failure that encompasses all 3 blood cell lineages, leading to peripheral pancytopenia and hypoplasia
- Symptoms relate to cytopenias, and include pallor, shortness of breath, fatigue, and potential bruising owing to low levels of platelets
- Infection, mouth sores, or an illness that does not improve may prompt a visit to the doctor’s office and subsequent diagnosis of aplastic anemia

PNH and Aplastic Anemia

- Aplastic anemia is closely related to PNH, and approximately 20% of patients with aplastic anemia have concurrent PNH at diagnosis
- The relationship between PNH and aplastic anemia has been proposed to arise from partially overlapping etiologies
- It is important to test for PNH in patients with aplastic anemia

Concurrent Presentation of Aplastic Anemia and PNH

- Not all patients with aplastic anemia have a subclinical PNH clone
- In patients with PNH, thrombosis can be severe and is a leading cause of death
- In PNH patients, the stress of hemolysis can lead to dyserythropoiesis
- Results from marrow tests must be evaluated in the appropriate clinical context

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