



Paroxysmal Nocturnal Hemoglobinuria (PNH): The Headache you Don't Want to Miss

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, noninherited clonal hematopoietic stem-cell disorder characterized by complement-mediated hemolysis, thrombosis, and variable bone marrow failure. Its presentation is heterogeneous and may lack visible hemoglobinuria. In this case report, we highlight a 38-year-old man who presented with persistent headache, fatigue, dizziness, anorexia, and unintentional weight loss. Examination showed pallor and tachycardia without focal neurologic deficits. Laboratory testing demonstrated profound pancytopenia, macrocytic anemia (hemoglobin 4.3 g/dL; mean corpuscular volume 113.3 fL), elevated lactate dehydrogenase, undetectable haptoglobin, and a negative direct antiglobulin test. Bone marrow biopsy was markedly hypocellular (15%-20%) with less than 5% blasts. Myeloid next-generation sequencing identified five somatic phosphatidylinositol glycan class A (PIGA) variants, and high-sensitivity flow cytometry demonstrated a PNH clone. The patient received red-cell transfusion, started ravulizumab as an outpatient, and was referred for allogeneic hematopoietic stem-cell transplantation evaluation. This case highlights that PNH should be considered in unexplained cytopenias with laboratory evidence of hemolysis, even without classic hemoglobinuria, and that diagnosis requires laboratory confirmation.

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal disorder of hematopoietic stem cells caused by somatic mutations in the phosphatidylinositol glycan class A (PIGA) gene, resulting in deficiency of glycosylphosphatidylinositol (GPI)-anchored complement regulatory proteins, most notably CD55 and CD59. The absence of these surface proteins renders affected blood cells susceptible to complement-mediated destruction, producing the hallmark triad of intravascular hemolysis, cytopenias, and thrombophilia. Thrombosis is the leading cause of morbidity and mortality in PNH, occurring in approximately 21% of patients, with a predilection for unusual venous sites including hepatic veins, mesenteric veins, and cerebral venous sinuses [1,2]. PNH has a peak incidence in the third to fifth decades of life, with most patients diagnosed between 30 and 50 years of age [3].

The clinical presentation of PNH is heterogeneous. Although the disease is named for episodic morning hemoglobinuria, this classic sign is present in only about one-quarter of patients at diagnosis [4]. Far more often the initial picture is dominated by cytopenias, fatigue, nonspecific constitutional symptoms, or thrombosis without visible hemolysis. As a result, the diagnosis is easily overlooked, particularly when the presenting complaint is itself common and usually benign. Headache is one such complaint, rarely a presentation of serious disease in isolation, yet occasionally can be the first clue to an underlying hematologic disorder or venous thrombosis. We report a case of PNH uncovered during the evaluation of a persistent occipital headache in a previously healthy 38-year-old man.

Case Presentation

A 38-year-old male with a history of mild thrombocytopenia of unclear etiology presented to the emergency department with a chief complaint of throbbing occipital headache that had not resolved with acetaminophen. He reported associated fatigue, dizziness, appetite loss, and an unintentional 7-pound weight loss. He denied fever, bleeding, chest pain, dyspnea, neck pain, photophobia, weakness, dysuria, nausea, vomiting, diarrhea, or recent travel. He had migrated to the U.S. 15 years ago from Asia after spending some time in a refugee camp.

Table 1: Peripheral blood and biochemical findings at presentation.

Test	Result	Reference ranges ¹¹
Hemoglobin	4.3 g/dL	13.5–17.5 g/dL (men)
Mean corpuscular volume	113.3 fL	80–100 fL
Red Cell Distribution Width	0.171	11.5–14.5%
Hematocrit	0.128	41–53% (men)
White blood cell count	$2.4 \times 10^3/\mu\text{L}$	$4.5\text{--}11.0 \times 10^3/\mu\text{L}$
Platelet count	$19 \times 10^3/\mu\text{L}$	$150\text{--}400 \times 10^3/\mu\text{L}$
Lactate dehydrogenase	587 U/L	110–210 U/L
Haptoglobin	Undetectable	16–199 mg/dL
Ferritin	1,088 ng/mL	30–300 ng/mL (men)
Vitamin B12	856 pg/mL	200–900 pg/mL
Direct antiglobulin test	Negative	Negative
Aspartate aminotransferase	47 U/L	10–40 U/L
Alanine aminotransferase	25 U/L	10–55 U/L
Total bilirubin	0.6 mg/dL	0.0–1.0 mg/dL
Direct bilirubin	0.2 mg/dL	0.0–0.4 mg/dL

On examination, he was tachycardic, otherwise hemodynamically stable and afebrile. He appeared pale but was in no acute distress. He had no hepatosplenomegaly, petechiae, palpable masses, or lymphadenopathy. He had a normal neurological exam.

Initial laboratory evaluation showed severe pancytopenia: hemoglobin 4.3 g/dL, platelets $19 \times 10^3/\mu\text{L}$, and white blood cell count $2.4 \times 10^3/\mu\text{L}$. The anemia was macrocytic with a mean corpuscular volume (MCV) of 113.3 fL. His serum haptoglobin was undetectable, Lactate dehydrogenase of 587 U/L. A comprehensive metabolic panel was unremarkable other than Aspartate aminotransferase (AST) of 47 U/L (Table 1). The patient was emergently transfused with 3 units of packed red blood cells and his hemoglobin stabilized at around 9 g/dL.

Given the severity of the pancytopenia in an otherwise healthy young adult, a broad differential diagnosis was formulated encompassing three major categories:

1. Infection: HIV, hepatitis B/C, tuberculosis, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), parvovirus B19, Lyme Disease, Sexually Transmitted Diseases
2. Hematologic disorder: Leukemia, lymphoma, bone marrow failure
3. Nutritional deficiency: Vitamin B12, folate, iron, copper deficiency

An extensive infectious workup was initiated. HIV, hepatitis panel, sexually transmitted disease panel, tuberculosis screening, EBV, CMV, parvovirus B19, and Lyme disease serologies were all negative. Computed tomography of the chest, abdomen, and pelvis was obtained to evaluate for hepatosplenomegaly, malignancy, or lymphadenopathy was negative. Folate levels were normal at 5 ng/mL and Vitamin B12 was at 856 pg/mL. Ferritin was elevated at 1,088 ng/mL, which in the context of pancytopenia raised concern for an underlying marrow process or inflammatory state.

The hematology-oncology service was consulted and recommended additional evaluation including copper levels,

Table 2: Tier 1 variants of known clinical significance PIGA mutations identified by myeloid next-generation sequencing.

PIGA cDNA variant	Protein consequence	Variant allele frequency
c.442C>T	p.Gln148*	0.121
c.690_701delinsCTGTC	p.Val231fs	0.049
c.1321_1345del	p.Phe441fs	0.039
c.553del	p.Ser185fs	0.024
c.108C>A	p.Cys36*	0.023

Table 3: PNH clone size by cell lineage on high-sensitivity peripheral-blood flow cytometry.

Cell population	PNH clone size
FLAER/CD157-deficient monocytes	0.727
FLAER/CD157-deficient neutrophils (granulocytes)	0.601
Total Type II and Type III CD59-deficient RBCs	0.072

peripheral blood smear review, direct antiglobulin test (DAT), bone marrow aspiration and core biopsy, cytogenetic studies, myeloid next-generation sequencing, and high-sensitivity peripheral-blood flow cytometry for PNH. Copper levels were within normal limits and the DAT was negative. Peripheral-blood smear showed no circulating blasts, no morphologic evidence of an acute leukemia, no schistocytes or spherocytes, and platelets were reduced without a reported morphologic abnormality.

The bone marrow biopsy was markedly hypocellular, with an estimated overall cellularity of 15%–20% and less than 5% blasts. The erythroid lineage showed megaloblastic maturation with a reversed myeloid-to-erythroid ratio, while megakaryocytes were reduced. Storage iron was present on biopsy. Routine cytogenetic studies were normal, and no clinically significant copy-number variants or copy-neutral loss of heterozygosity were identified. Myeloid next-generation sequencing of the bone marrow identified five Tier 1 PIGA variants predicted to disrupt normal PIGA function (Table 2). The mutations were detected with variant allele frequency (VAF) ranging from 12.1% to 2.3%.

High-sensitivity peripheral-blood flow cytometry detected PNH phenotypes in the erythrocyte, monocyte, and granulocyte lineages. CD157-deficient cells comprised 72.7% of monocytes and 60.1% of neutrophils, demonstrating a large PNH clone within the white-cell lineages (Table 3). CD157 is a GPI-anchored surface protein used as a surrogate for GPI functionality. The total CD59-deficient red-cell population was 7.2% (Table 3). The smaller red-cell clone relative to the monocyte and neutrophil clones may reflect ongoing hemolysis and dilution from the recent transfusion of normal red blood cells. In combination with the biochemical evidence of hemolysis, pancytopenia, hypocellular marrow, and multiple somatic PIGA variants, these findings supported the diagnosis of PNH associated with suspected aplastic anemia overlap.

Although the patient's occipital headache improved after transfusion and correction of his severe anemia, it did not completely resolve. Given the recognized association between PNH and thrombosis at unusual sites, the persistent headache raised concern for cerebral venous sinus thrombosis. Magnetic resonance imaging of the brain with venous imaging was therefore performed and showed no evidence of cerebral venous thrombosis or other acute intracranial abnormality.

Following diagnosis, the patient was monitored with serial hemoglobin measurements, which remained stable after transfusion. He was discharged with close outpatient hematology follow-up. Outpatient treatment consisted of starting ravulizumab and referral for allogeneic bone marrow transplantation to address the aplastic anemia.

Discussion and Conclusion

Paroxysmal nocturnal hemoglobinuria (PNH) is classically conceptualized as a triad of intravascular hemolysis, thrombophilia, and variable bone marrow failure, but the extent of each component varies widely between patients, and the clinical picture in an individual patient may shift over the course of their illness. The classic sign of morning hemoglobinuria that gives the disease its name is present in only about 25% of patients [4]. More commonly, patients report nonspecific symptoms such as fatigue, dyspnea, abdominal pain, dysphagia, and erectile dysfunction [4]. The historical term is therefore potentially misleading, as hemoglobinuria is neither universal nor necessarily nocturnal. A more accurate name for PNH could be "acquired GPI-anchor deficiency disorder" or "complement-mediated clonal hemolytic anemia".

PNH is best understood not as a single entity but as a spectrum defined by the International PNH Interest Group, comprising three major groups. Classic PNH features intravascular hemolysis without evidence of another marrow disorder and represents roughly one-third of patients with a detectable clone. The second group is PNH with hemolysis in the setting of another bone marrow failure syndrome. This group represents two thirds of patients with PNH and where our patient falls. The third group is subclinical PNH with small GPI-deficient populations and without hemolysis [5]. Clone size correlates with, though does not rigidly define, disease category: large granulocyte/monocyte clones (>50%) typically found in classic hemolytic disease and clones below ~10% are characteristic of the marrow-failure subtype [6]. Our patient's large leukocyte clones are consistent with clinically significant disease, while the smaller erythrocyte clone (7.2%) partly reflects ongoing hemolysis and dilution by transfused normal red cells.

This nonspecificity and heterogeneity in presentation leads to significant diagnostic delays. One study using Japanese insurance claim data reported that median time from symptom onset to definitive diagnosis was 26.5 months, and that longer intervals were associated with higher rates of complications including thrombosis at unusual anatomic sites and renal failure [7]. The rarity of PNH likely contributes to this delay because many nonspecialist clinicians encounter few, if any, cases during their careers and may be unfamiliar with the findings that should prompt PNH testing [4]. Our patient exemplifies this diagnostic challenge: He presented not with the textbook symptom of nocturnal hemoglobinuria or dark urine in the morning but with a persistent headache that upon further workup was diagnosed with PNH.

Though PNH patients can have a complex clinical course, it is essential that a diagnosis is made in a timely manner to limit mortality and morbidity secondary to thrombosis.

Thromboembolic events are reported in up to 43% of patients at disease onset, frequently at unusual sites such as the hepatic (Budd-Chiari), mesenteric, and cerebral veins, and often as the presenting event [1]. The recognized predilection for cerebral venous sinus thrombosis was the reason why our patient's incompletely resolving

headache warranted dedicated venous imaging of the brain.

Complement inhibition is the foundation of treatment for clinically significant hemolytic PNH. Eculizumab and the longer-acting ravulizumab suppress terminal complement-mediated intravascular hemolysis and reduce thrombotic risk. Long-term ravulizumab data show durable control of intravascular hemolysis and a low incidence of major adverse vascular events [8]. In a 2043-patient-year analysis, complement inhibition roughly halved the thrombosis rate compared with untreated patients [1]. Patients receiving terminal complement inhibitors require vaccination against meningococcal disease and counseling regarding the residual risk of serious infection; antimicrobial prophylaxis should follow the applicable product labeling and local or national guidance rather than being presented as universal lifelong therapy [8]. There are no clearly established guidelines in regards to anticoagulation in PNH [1]. Anticoagulation is indicated for an acute thrombotic event and may be used for selected primary or secondary prophylaxis.

Lastly, complement inhibition treats complement-mediated hemolysis but does not correct the underlying aplastic marrow. Allogeneic hematopoietic stem cell transplantation remains the only curative option and the only intervention that can eradicate the PNH clone and restore normal hematopoiesis [9]. Transplantation is not recommended for hemolytic PNH or for thromboembolic disease alone, as outcomes in patients transplanted for thrombosis have historically been poor [10]. The patient's referral for transplant evaluation was therefore driven principally by the suspected aplastic anemia overlap given the profound pancytopenia and marrow hypocellularity.

In conclusion, PNH is a diagnostically complex disorder whose nonspecific and often atypical presentations contribute to diagnostic delays and preventable morbidity. This patient presented with headache, fatigue, and constitutional symptoms rather than the classic hemoglobinuria, and it was the recognition of profound pancytopenia with laboratory evidence of hemolysis that ultimately led to the diagnosis. We do not advocate extensive hematologic testing for every headache. Rather, this case illustrates that common, benign-appearing symptoms must be interpreted alongside objective data and the overall clinical picture. A seemingly simple headache, when accompanied by constitutional symptoms and severe cytopenias, may be the manifestation of a life-threatening disorder requiring specialist evaluation and lifelong surveillance.

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Note: The patient provided consent for this case report.

References

1. Gurnari C, Awada H, Pagliuca S, Dima D, Ullah F, Kawashima N, et al. Paroxysmal nocturnal hemoglobinuria-related thrombosis in the era of novel therapies: a 2043-patient-year analysis. *Blood*. 2024;144(2):145-55.
2. Devalat B, Mullier F, Chatelain B, Dogné JM, Chatelain C. Pathophysiology, diagnosis, and treatment of paroxysmal nocturnal hemoglobinuria: a review. *Eur J Haematol*. 2015;95(3):190-8.
3. Richards S, Dickinson A, Cullen M, Griffin M, Munir T, McKinley K, et al. Presentation clinical, haematological and immunophenotypic features of 1081 patients with GPI-deficient (paroxysmal nocturnal haemoglobinuria)

- cells detected by flow cytometry. *Br J Haematol.* 2020;189(5):954-66.
4. Röth A, Maciejewski J, Nishimura J-I, Jain D, Weitz J. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol.* 2018;101:3–11.
 5. Panse J. Paroxysmal nocturnal hemoglobinuria: Where we stand. *Am J Hematol.* 2023;98(S4):S20-32.
 6. Babushok D. When does a PNH clone have clinical significance? *Hematology Am Soc Hematol Educ Program.* 2021;2021(1):143-52.
 7. Ueda Y, Kawaguchi T, Ikezoe T, Shimono A, Hayashi H, Uchiyama M, et al. Diagnostic delay and clinical outcomes of paroxysmal nocturnal hemoglobinuria: a retrospective cohort study using Japanese claims data. *Int J Hematol.* 2026 Aug 18.
 8. Kelly RJ, Holt M, Szer J. Pharmacological Therapies in Paroxysmal Nocturnal Haemoglobinuria: Focus on Complement Inhibition. *Drugs.* 2025;85(11):1413-28.
 9. Ussowicz M, Przystupski D, Mensah-Glanowska P, Piekarska A. Current status and perspectives of hematopoietic cell transplantation in patients with paroxysmal nocturnal hemoglobinuria. *Front Immunol.* 2025;15:1521484.
 10. Patriquin C, Kiss T, Caplan S, Chin-Yee I, Grewal K, Grossman J, et al. How we treat paroxysmal nocturnal hemoglobinuria: A consensus statement of the Canadian PNH Network and review of the national registry. *Eur J Haematol.* 2019;102:36–52.
 11. Kratz A, Ferraro M, Sluss P, Lewandrowski K. Normal Reference Laboratory Values. *N Engl J Med.* 2004;351(15):1548-63.