fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Paroxysmal Nocturnal Hemoglobinuria (PNH) in a Young Adult: A Diagnostic Challenge with Recurrent Abdominal Pain and Fatigue Mimicking Gastrointestinal Malignancy

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder marked by destruction of red blood cells, low blood counts, and an increased risk of unusual blood clots. Symptoms vary but often include fatigue, dark urine from hemolysis, and clot-related complications. Diagnosis is made using flow cytometry and FLAER testing. Historically, care focused on supportive treatment and managing clots. However, recent advances, such as hematopoietic stem cell transplantation and complement inhibitors like eculizumab, have significantly improved outcomes. Here we report a 26-year-old male having the clinical features of recurrent abdominal pain, fatigue, and left lower leg swelling, which are clinically consistent with paroxysmal nocturnal hemoglobinuria (PNH). Differentials were ruled out by appropriate investigation, and the case was confirmed by flow cytometry. Having been diagnosed, our patient started treatment with the complement inhibitor eculizumab. Resolution of the abdominal pain and normalization of clinical parameters were noted within 3 weeks of treatment initiation.

Keywords: Paroxysmal nocturnal hemoglobinuria (PNH); Hemolysis; Dark-Urine; Recurrent abdominal pain

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and progressive hematopoietic stem cell disorder in which hematopoietic cells are deficient in glycosylphosphatidylinositol (GPI), leading to a lack of the complement inhibitor proteins CD55 and CD59 on the surface of blood cells, which subsequently causes characteristic intravascular complement-mediated hemolysis, bone marrow failure, along with platelet activation and aggregation [1][2]. Its diverse clinical manifestations often pose significant diagnostic challenges, leading to delays in appropriate management. Previous reports suggest that the incidence of clinically significant diseases is in the range of 1 to 10 cases per million population, and it is chiefly a disease of adults, and the peak age of onset in the thirties [3]. The etiology and symptoms of PNH are similar in Asian and Western patients, but it has been proposed that the clinical course of the disease may differ between the ethnic groups [4]. It is evident that patients with PNH have an approximately 62-fold greater risk of thrombosis compared with the general population [5] and an estimated 10.2-fold increase in mortality risk [6]. The most common sites of thromboembolism are the liver, kidney, brain, and gut, and up to 44% of patients with PNH experience a clinically evident thrombosis [5,7]. Although PNH is caused by a mutation of a gene on the X chromosome, it affects males and females equally [8]. Here we report a case of a 26-year-old

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Citation: Suvarthy Dey, Abdullah Al Masud, Abdullah Al Jubaer, Kazi Nusrat Jahan Bristy, Chandrima Halder, Tasnim Mostafa, Sheikh Sophia Shaubnaum, Sonia Sarmin, Avijit Sarker Jyoti. Paroxysmal Nocturnal Hemoglobinuria (PNH) in a Young Adult: A Diagnostic Challenge with Recurrent Abdominal Pain and Fatigue Mimicking Gastrointestinal Malignancy. Fortune Journal of Health Sciences. 8 (2025): 1052-1056.

Received: October 27, 2025
Accepted: November 06, 2025
Published: November 11, 2025

Dey S, et al., Fortune J Health Sci 2025
DOI:10.26502/fjhs.368

male who experienced extreme fatigue for 25 days, recurrent abdominal pain for 20 days, and left lower leg swelling for 2 days, accompanied by bi-cytopenia, anemia, jaundice, and thickened intestinal and colonic wall as well.

Case Presentation

Mr. X, a 24-year-old male who is normotensive, non-diabetic, and a non-smoking shopkeeper, was admitted to "Y" hospital on June 5, 2024, with complaints of fatigue for 25 days, recurrent abdominal pain for 20 days, and painful swelling of the left lower leg for 2 days. According to the statement of the patient, he was reasonably well 25 days ago, then developed fatigue that gradually worsened each day, persisted all day for the last 7 days, and caused tiredness with mild regular activities. This fatigue was not associated with palpitations, shortness of breath, or diurnal variation. He also complained of recurrent mid-abdominal pain that was intermittent, non-radiating, colicky in nature, and mild to moderate in severity for the past 20 days. There was no epigastric burning or features of malabsorption. The pain worsened after eating, accompanied by a feeling of early satiety, and was partially relieved by antispasmodics. Occasionally, the pain was associated with nausea and vomiting, which was non-projectile, non-foul-smelling, and not blood- or bile-stained. Upon further inquiry, the patient reported repeated episodes of jaundice over the last 1.5 years, characterized by yellow discoloration of the skin and sclera, along with dark urine. There were no itching, pale or dark stools, skin hyperpigmentation, tremors, or other neurological features. He stated that each episode was resolved spontaneously without definitive treatment. The most recent episode was about 2 months ago. The patient also reported occasional passage of sticky, offensive, black tarry stools, with a few episodes over the past 1.5 years, the last occurring about 3 months ago, but without any hematemesis. He also complained of painful swelling of the left lower leg for 2 days, which was associated with heaviness, localized pain, raised temperature, and skin discoloration. The pain was sudden in onset, mild to moderate, constant, throbbing in nature, with no reported aggravating or relieving factors. He mentioned that the pain began following IV cannulation performed through the affected leg for a few days.

Regarding past illnesses, he recalled a 15-day episode of low-grade, intermittent fever about a week ago, associated with chills and rigor, but no evening fever rises or night sweats. It subsided after taking antipyretics. The fever was associated with abdominal pain but no jaundice, altered bowel habits, urinary symptoms, or other systemic issues. Aside from this, he reported no history of TB or contact with known TB patients. He said none of his family members were suffering from a similar illness. There is no family history of jaundice, consanguinity, TB, bronchial asthma, ischemic heart disease, chronic liver disease, or chronic kidney disease. The patient has been married for 1.5 months. He denied any history of IV drug abuse, sharing needles, or tattooing. He also denied any sexual activity with multiple partners or unusual sexual practices like homosexuality. The patient comes from a middle socio-economic background, residing as a tenant in a four-storied building with good sanitation and access to safe drinking water. Upon inquiry, he stated that he had lived in Saudi Arabia for 8 years, where he was working in the family's clothing business. Now, he has returned to his home country about 1.5 months ago permanently. He was immunized according to the EPI schedule and received three doses of the COVID-19 vaccine. During his admission to a private hospital, he was prescribed paracetamol, antispasmodics, anti-emetics, PPIs, injectable antibiotics (names unknown), and oral medications such as rifaximin 550 mg, mesalazine 800 mg, Silamyrin 500 mg, and ursodeoxycholic acid 300 mg, as per the clinician's judgment for symptomatic improvement. Additionally, he also reported using herbal medications on two occasions in the last 6 months to manage symptoms of jaundice. On general examination, the patient was found ill-looking, with average body build and nutrition, moderately anemic and mildly icteric, with unilateral pitting edema of the left lower leg. Vitals were found normal (Pulse 92 b/m, BP 100/60 mmHg, Temp. 99 ◦F, R/R 15 breaths/min). On systemic examination, the abdomen was normal on inspection with mild tenderness over the umbilical region on palpation. There was no organomegaly, palpable mass, or lymph nodes, with no evidence of ascites. Bowel sound was present without hepatic bruit or splenic rub. Examination of other systems revealed no abnormality.

On local examination of the left lower limb, there was a tender swelling with signs of inflammation, and purplish-blue discoloration of the skin of the left lower leg. No visible muscle wasting or deformity was noted. The patient was advised to store his urine for the whole night, and it was found to be dark brown (Figure 1).

Figure 1: Collected Urine of the patient

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Several investigations were carried out to establish the diagnosis. The patient demonstrated persistent anemia, with hemoglobin levels fluctuating between 4.6 g/dl and 9.2 g/dl during one month of evaluation (Table 1A). Peripheral blood film (PBF) revealed variable degrees of bi-cytopenia, characterized by normocytic normochromic anemia with associated thrombocytopenia and leukopenia. Clinical evidence of jaundice was supported by persistently elevated serum bilirubin levels ranging from 3.0 to 2.0 mg/dl over the course of the month, with a predominance of indirect hyperbilirubinemia (Table 1B).

Table 1A: CBC report over 1 month.

CBC	28.05.2024	30.05.24	06.06.24	27.06.24
Hb%	4.6	8.3	10.7	9.2
ESR	99	48	31	25
RBC	1.68	2.88	3.64	3.19
WBC	2200	4600	7000	4600
Neutrophil	52%	75%	48%	32%
Lymphocyte	31%	22%	48%	62%
Eosinophil	5%	1%	1,93,000	1%
Monocyte	7%	2%	92.5	10%
Basophil	0%	0%	0%	0%
Platelets	1,50,000	1,20,000	1,17,000	1,93,000
MCV	82	84	90.4	92
MCH	27.4	28.7	30	28.8
MCHC	33.4	34.3	32.5	31.5

Table 1B: Biochemical reports over 1 month.

Liver Function Test	29.05.24	31.05.24	09.06.24	27.06.24
S. Bilirubin	3.0 mg/dl	1.9 mg/dl	1.78 mg/dl	2 mg/dl
Direct	0.6 mg/dl	0.3 mg/dl	0.43 mg/dl	0.56 mg/dl
Indirect	2.4 mg/dl	1.6 mg/dl	1.35 mg/dl	1.44 mg/dl
SGPT	29 U/l	47 U/l	33 U/l	50 U/l
SGOT	76 U/l	60 U/l	63 U/l	77 U/l
ALP	157	144	175	158
Prothrombin time	15 sec	14 sec	14 sec	13 sec
Total protein	5.5 g/dl	5.3 g/dl	5.1 g/dl	5.6 g/dl
S. albumin	3.8 g/dl	3.9 g/dl	3.6 g/dl	3.8 g/dl

Additional investigations showed a serum LDH of 257U/L, reticulocyte counts of 1.2% (09.06.24) and 1.4% (27.06.24), ESR of 21mm/hour, and CRP of 18mg/dl. Procalcitonin was within normal limits at 0.2 ng/dl. D-dimer was elevated, with values of 2.2µg/ml (06.06.24) and 1.52µg/ml (09.06.24). These findings were suggestive of a hemolytic process with evidence of ineffective erythropoiesis and bone marrow suppression, accompanied by an inflammatory response. The PNH clone was confirmed by flow cytometry, demonstrating the absence of CD24, CD55, and CD59 on granulocytes and monocytes. Routine investigations, including blood glucose and renal function tests, were within normal limits. Urine analysis initially revealed 3-6 pus cells/PHF but normalized following seven days of hospital treatment. Microbiological and serological investigations, including repeated blood and urine cultures, Widal test, Weil-Felix test, Brucella serology, hepatitis panel, VDRL, and HIV testing, were all unremarkable. Imaging studies revealed additional organ involvement. Abdominal ultrasonography demonstrated features of acute hepatitis and a thickened gallbladder. Chest X-ray (P/A View) was normal. Contrast-enhanced CT of the abdomen showed mild hepatosplenomegaly and intermittent full-thickness thickening of the small intestinal wall with edema-like contrast enhancement. Upper GI endoscopy and

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colonoscopy were unremarkable. Doppler ultrasonography of the left lower limb revealed thrombophlebitis without evidence of deep vein thrombosis. Taken together, the patient was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) complicated by thrombophlebitis of the left lower leg. The clinical and laboratory findings highlight the hemolytic nature of the disease, associated marrow suppression, and thrombotic complications, and the patient was managed according to established treatment protocols for PNH and thrombophlebitis (Table 2).

Blood Test Results comparison

Table 2: PBF analysis report for entire one month

Anemia Type	29.05.24	31.05.24	06.06.24	27.06.24
Anemia Type	Normocytic normochromic with anisocytosis	Normocytic normochromic with anisocytosis	Normocytic normochromic	Normocytic normochromic
Other Deficiency 1	Leucopenia	Thrombocytopenia	Thrombocytopenia	N/A
Other Deficiency 2	N/A	N/A	N/A	N/A

Discussion

PNH is characterized by low blood cell counts (anemia, thrombocytopenia, neutropenia), which can be a sign of bone marrow disorders, including some types of cancer [2]. PNH involves excessive hemolysis, which can lead to elevated levels of lactate dehydrogenase (LDH) and other markers that may mimic some other conditions, including some types of cancer and recurrent intestinal ischemia [9]. In PNH, there is destruction of RBC, which releases Hb into blood bloodstream, it is filtered by the kidneys and broken which gives dark coloration of urine. On the contrary, In GI malignancy, the bile duct can be blocked by a malignant tumor, which may cause stagnation of bilirubin, ultimately causing dark urine [2]. PNH presenting as a diagnostic challenge with recurrent abdominal pain and fatigue, potentially mimicking gastrointestinal malignancy, is a well-documented issue due to the non-specific nature of PNH symptoms, particularly those related to thrombophlebitis without evidence of deep vein thrombosis. Our case details recurrent episodes of abdominal pain accompanied by fatigue associated with dark urine, which mimics an abdominal malignancy. Despite the diagnostic dilemma, having strong clinical suspicion, ruling out the malignancy, and establishing our diagnosis was the nobility of our case. PNH can manifest as abdominal pain by blocking the gut vessels with microthrombi [9]. The dark urine and recurrent abdominal pain increased the diagnostic dilemma of our case with GI malignancy, which was finally cleared by meticulous clinical examination and analysis of the investigation report. In our case, though there was severe recurrent abdominal pain, there was no evidence of thrombosis, evidenced by a normal D-dimer value. Possible explanation of recurrent abdominal pain in our PNH patient might be that excessive hemoglobin released into the bloodstream because of PNH, might lead to the consumption of endothelium-derived nitric oxide at a rate of 600-fold faster than normal [10]. The depletion of nitric oxide prevents the dilatation of smooth muscle fibers, causing recurrent abdominal pain and vasoconstriction with decreased blood flow [11,12]. The platelet activation and aggregation, endothelial swelling, and impaired fibrinolysis all might contribute to recurrent abdominal pain in PNH patients, other than gut vessel occlusion by microthrombi [13,14]. Previous studies demonstrated that those patients with PNH who experience abdominal pain have a 3.6-fold increased risk of thrombosis and a 2.2-fold risk of premature mortality [15]. In our case, LDH and haptoglobin values indicated the hemolytic anemia, and the clinical findings were consistent with the abdominal malignancy, but the PNH flow cytometry confirmed the final diagnosis, which is strengthened by a similar presentation from another published report [2]. It is evident that treatment with eculizumab reduces endothelial activation and markers of thrombin generation, exploring the association between an inflammatory, prothrombotic state and chronic complement activation in PNH patients [16]. In our case, following confirmation of PNH and the initiation of therapy with eculizumab, hemolysis was significantly reduced, the hemolysis-mediated abdominal pain resolved completely, and the patient no longer suffered from the severe fatigue that had previously restricted his activities. A similar consequence was observed in a previous study, which strengthens our case findings [2]. Having fatal consequences of PNH, this case emphasizes the importance of conducting a full clinical assessment of abdominal pain and acknowledging the abdominal pain as a risk factor for thrombotic events in patients with PNH.

Conclusion

Paroxysmal Nocturnal Hemoglobinuria (PNH) remains a rare but significant diagnostic challenge, particularly in young adults presenting with nonspecific symptoms like recurrent abdominal pain and fatigue. This case underscores the importance of maintaining a high index of suspicion for PNH in patients with such symptoms, especially when they mimic more common conditions like gastrointestinal malignancy. Early recognition and accurate diagnosis are critical in preventing life-threatening complications and ensuring

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timely, targeted therapy. This case highlights the need for a multidisciplinary approach and vigilance in evaluating atypical presentations to improve patient outcomes in rare hematological disorders like PNH.

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