Clinical Medical Insights: Blood Disorders

REVIEW

Hemoglobinuria Misidentified as Hematuria: Review of Discolored Urine and Paroxysmal Nocturnal Hemoglobinuria

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Abstract: Discolored urine is a common reason for office visits to a primary care physician and urology referral. Early differentiation of the type or cause of discolored urine is necessary for accurate diagnosis and prompt management.

Paroxysmal nocturnal hemoglobinuria is a clonal disorder caused by acquired somatic mutations in the PIG-A gene on the X-chromosome of hemopoietic stem cells and leads to deficiency of surface membrane anchor proteins. The deficiency of these proteins leads to an increased risk of hemolysis of erythrocytes and structural damage of platelets, resulting in a clinical syndrome characterized by complement-mediated intravascular hemolytic anemia, bone marrow failure, and venous thrombosis. Patients with this clinical syndrome present with paroxysms of hemolysis, causing hemoglobinuria manifesting as discolored urine. This can be easily confused with other common causes of discolored urine and result in extensive urologic work-up. Three commonly confused entities of discolored urine include hematuria, hemoglobinuria, and myoglobinuria. Specific characteristics in a dipstick test or urinalysis can guide differentiation of these three causes of discolored urine.

This article begins with a case summary of a woman presenting with cranberry-colored urine and a final delayed diagnosis of paryxysmal nocturnal hemoglobinuria. Her hemoglobinuria was misdiagnosed as hematuria, leading to extensive urologic work-up. The article also gives an overview of the approach to diagnosing and treating discolored urine.

Keywords: discolored urine, hematuria, hemoglobinuria, myoglobinuria, paroxysmal nocturnal hemoglobinuria, GPI-AP (glycosylphosphatidylionositol—anchor proteins), CD55, CD59

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Clinical Significance

Discolored urine is a common symptom and presentation in outpatient and inpatient practice. This article begins with a case presentation, which is followed by a detailed overview of discolored urine and paroxysmal nocturnal hemoglobinuria (an easily overlooked condition).

Case Presentation

A woman in her 80s was admitted to an inpatient medical service at a tertiary care medical center in the Boston area with cranberry-colored urine. Further history revealed intermittent episodes of dark-colored urine for several years. She had no dysuria or frequency, no abdominal, flank or supra-pubic pain, and no history of kidney stones. Her past medical history included hypothyroidism treated with thyroid supplements, gastric erosions, Alzheimer's dementia treated with Donepezil, myelodysplastic syndrome (with chronic anemia and thrombocytopenia dating back 5 years) treated with erythropoietin supplementation, and chronic inflammatory demyelinating polyneuropathy treated with monthly IV Immunoglobulin injections. She was not a smoker and had no family history of cancers. Vital signs and physical examination were unremarkable. Upon further review, there was no evidence of blood in her stools or post-menopausal bleeding.

Laboratory data was abnormal, with a hemoglobin of 9.9 g/dL and hematocrit of 29.3% (mean corpuscular volume of 107.2 fL, mean corpuscular hemoglobin of 36.5 pg and red cell distribution of width of 23.6 percent); platelet cell count of 69,000 per mm^3. Urine was red and cloudy, with a specific gravity of 1.019 and pH of 6.0, positive (trace) for ketones, positive (+) for leukocytes, positive (++) for protein, and positive (+++) for blood. No bacteria, glucose, bilirubin, or urobilinogen were detected. The sediment contained 2–5 red blood cells (RBCs) and no white blood cells (WBCs) per high-power field (HPF).

In imaging studies, abdominal and pelvic computed tomography (intravenous contrast-enhanced) showed multiple renal cysts with no evidence of obstruction. There was no evidence of solid renal mass and no renal, ureteral, or bladder stones. Retroperitoneal ultrasound showed normal kidney size and contour, no renal calculi or hydronephrosis, and fullness of the upper pole of the right collecting system that was radiologically consistent with a parapelvic cyst. A survey scan of the bladder was unremarkable.

Chronologic review of the patient's previous records confirmed evidence of blood and RBCs in her urine dating back 6 years before admission. Following the first episode of blood in the urine, she was referred to the urologist with a diagnosis of painless hematuria and had been receiving regular work-up since, including normal cystoscopies and urine cytology.

Analysis of patient's urine over the last few years (Table 1) revealed the persistent presence of blood with an intermittent presence of RBC's. Evidence of previous episodes (April 2002 and March 2005, Table 1) of urinary tract infections (UTIs) in this patient may explain some of the episodes of blood and RBCs in the urine, but not the persistent findings. Her findings were consistent with hemoglobinuria or myoglobinuria (Fig. 1). The patient had no risk factors for developing myoglobinuria (Fig. 3). This raises high clinical suspicion for hemoglobinuria (Fig. 3).

Further evaluation revealed a reticulocyte count of 4.1% (0.8%–1.8%), absolute reticulocyte count of 107 K/μL (50–75), lactate dehydrogenase (LDH) of 1895 U/L (0–250), haptoglobin of <10 mg/dL (34–200), 24-h urine protein of 36 mg/dL (<10 mg/dL), 24-h urine creatinine of 40.6 mg/dL (24–392 mg/dL), complement levels were normal, serum iron of 49 μg/dL (60–160), total iron-binding capacity of 274 μg/dL (275–425), negative Coombs' test, and no growth on urine culture. Due to the presence of iron deficiency anemia with a high reticulocyte count and no evidence of hemolysis, blood in the urine with lack of RBCs on repeated urine analysis, hemoglobinuria was suspected (as will be discussed later). Based on the patient's history and lab values, clinical suspicion was high for paroxysmal nocturnal hemoglobinuria, which was thought to be the cause of her recurrent discolored urine. The following tests confirmed the diagnosis: leukocyte alkaline phosphatase score of zero (11–95), sucrose lysis test was positive, flow cytometry of peripheral blood showed loss of CD55 and CD59 in the granulocytes, ruling out paroxysmal nocturnal hemoglobinuria (PNH), for which both CD55 and CD59 expression should be >90%. Additionally, magnetic resonance imaging (MRI) of the kidneys showed diminished T1 and T2 weighted signal intensity involving the cortex of both kidneys, which is consistent with iron deposition in the renal cortex. No renal masses or cysts were detected. The pattern of iron deposition involving only the renal cortex is

Table 1. Urinalyses.

	May 2005	Mar 2005	Oct 2004	Jul 2004	Nov 2003	Aug 2003	Jul 2003	Apr 2002
Color	Normal	Normal	Red	Normal	Red	Red	Normal	Normal
Character	Cloudy	Cloudy	Cloudy	Clear	Cloudy	Turbid	Cloudy	Cloudy
Specific gravity	1.021	1.015	1.019	1.015	1.013	1.015	1.024	1.025
PH	5.0	5.5	6.0	5.0	7.5	5.0	6.5	6.0
Protein	+	+	++	+	+++	–	+	–
Glucose	–	–	–	–	–	–	–	–
Ketone	–	–	Trace	–	Trace	–	–	–
Bilirubin	–	–	–	–	–	–	–	–
Blood	+++	+++	+++	+++	+++	+++	+++	+++
Urobilinogen	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Leukocyte	+	+	+	–	Trace		+	++
Nitrite	–	–	–	–	+	–	–	+
WBC/HPF	None	2–5	None	0–2	None	0–2	0–2	10–25
RBC/HPF	None	0–2	2–5	None	0–2	2–5	None	5–10
Bacteria	Trace	+	+	–	++	–	–	+++
Crystals	–	–	–	–	–	–	–	–
Casts	Rare granular	–	–	–	–	–	Rare granular	–

consistent with PNH.[1,35–37] An MRI of the liver, spleen, and pancreas showed normal signal intensity.

The patient was managed conservatively with supportive care and frequent blood transfusions.

Discussion

Discolored urine

Discolored urine is a common cause for office visits to an internist and referral to a urologist. It is also one of the most common reasons for urology consultation in hospitalized patients. Discolored urine can occur in various conditions or situations. One of the common causes of blood in urine among hospitalized patients is catheterization-associated trauma from an indwelling Foley catheter.

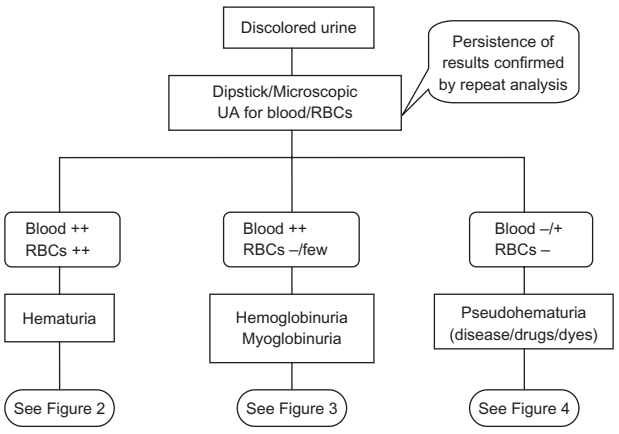

Figure 1. Overview and classification of discolored urine. Cause of discolored urine divided into three groups based on the urinalysis.

The term hematuria is commonly misused to describe dark urine. Typically, other causes of red/brown urine are misdiagnosed as hematuria. Causes of discolored urine can be broadly classified into: hematuria, hemoglobinuria, myoglobinuria, and pseudohematuria (non-pathological causes of discolored urine). Hemoglobinuria and myoglobinuria can be difficult to differentiate from hematuria. Clues in dipstick/urinalysis that help differentiate the causes of discolored urine are illustrated in Figure 1.

Detection of blood on the dipstick test and the presence of a proportionate number of RBCs on microscopic urinalysis (UA) are indicative of hematuria. If blood is detectable with no or very few microscopically visible RBCs, the presence of pigment, hemoglobin, or myoglobin, in the urine is indicated. Other causes of discolored urine, with/without detection of blood and without RBCs, are observed following ingestion of some drugs/dyes. Additionally, when the urine sample is centrifuged, the sediment is red in hematuria and the supernatant is red in hemoglobinuria, myoglobinuria, or drug/dye-induced discoloration.

Dipstick positive + proportionate number of RBCs on microscopic UA = hematuria (Fig. 2 outlines various etiologies of hematuria).

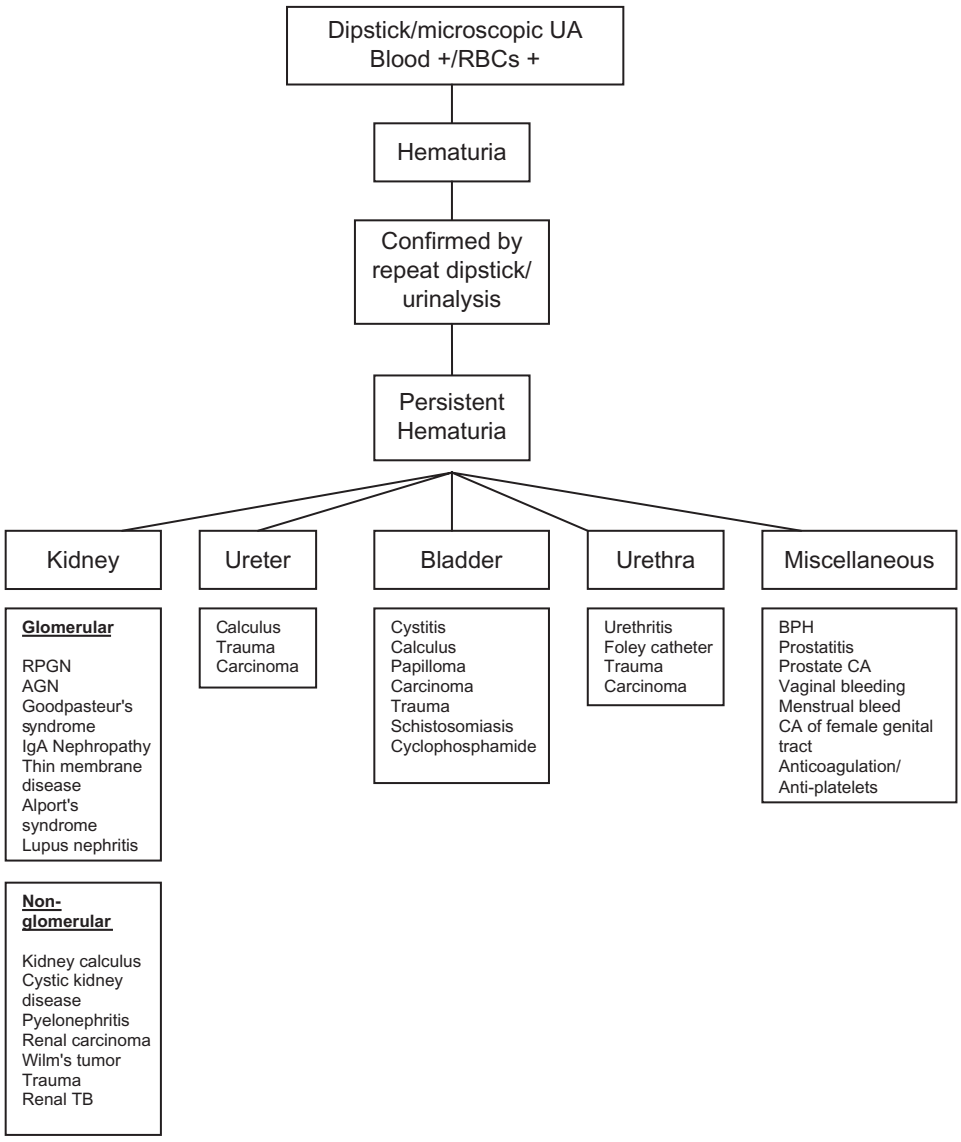

Figure 2. Causes of hematuria.
Abbreviations: RPGN, Rapidly progressing glomerulonephritis; AGN, Acute Glomerulonephritis.

Dipstick positive + disproportionately low or absent RBCs on microscopic UA = hemoglobinuria/myoglobinuria (Fig. 3 outlines various etiologies of hemoglobinuria and myoglobinuria).
Dipstick negative (rarely 1+) + no RBCs on microscopic UA = pseudohematuria (Fig. 4 outlines various etiologies of pseudohematuria).

During the dipstick test on a urine sample to evaluate for the presence of blood, the reagent on the test strip detects the presence of pigment in the urine sample. This pigment can be hemoglobin (Hb) or myoglobin (Mb); other pigments such as bilirubin and urobilinogen are not part of this discussion. In the past, the presence of intact RBCs in the urine without any free pigment could not be detected using the urine test strip reagent. Hence, one could have a dipstick negative for occult blood but microscopy could be positive for RBC. Currently, intact RBCs are allowed to lyse while on the test strip for subsequent detection of hemoglobin pigment released from these lysed RBC. The pigment (Hb or Mb) acts as a catalyst for the oxidation of an indicator by organic peroxide on a test strip. Examples of indicator-peroxide combinations on test strips include 3, 3′, 5, 5′-tetramethylbenzidine—cumene hydroperoxide, 3, 3′, 5, 5′-tetramethylbenzidine—2, 5-dimethyl-2, 5-dihydroperoxyhexane, and 3, 3′, 5,

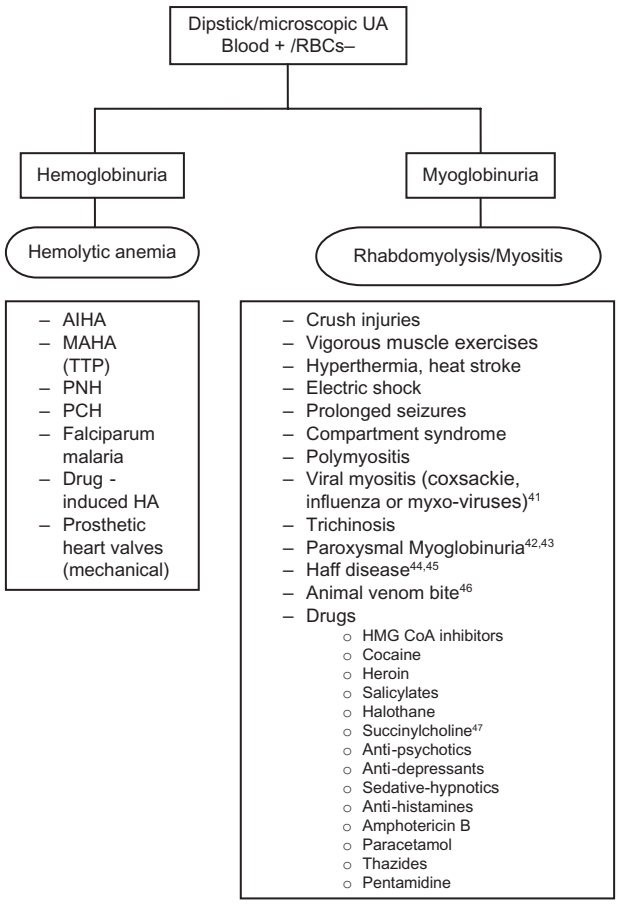

Figure 3. Hemoglobinuria and Myoglobinuria.
Abbreviations: AIHA, Autoimmune hemolytic anemia; MAHA, microangiopathic hemolytic anemia; TTP, Thrombotic thrombocytopenia purpura; PNH, Paroxysmal nocturnal hemoglobinuria; PCH, Paroxysmal cold hemoglobinuria.

5′-tetramethylbenzidine—diisopropylbenzene dihydroperoxide. The dipstick bottles have different color coding charts depending on the manufacturer.

The dipstick test can give a false-negative result for blood when levels of ascorbic acid are high in the urine. This is of particular importance for patients taking supplemental vitamin C daily. The test should be conducted after limiting the vitamin C dose for 1–2 days.

The dipstick test can also give false-positive results for blood when the urine sample is contaminated with oxidizing chemicals such as hypochlorites, which may be used in cleaning solutions, bacterial peroxidases released by bacterial colonization in the urine, and menstrual blood in women.[2]

Once the dipstick test strip detects the presence of pigment in the urine sample, the next step is to differentiate the type of pigment. Hb and Mb can be differentiated using an ammonium sulfate test. A mixture of ammonium sulfate and urine sample is centrifuged. Ammonium sulfate precipitates Hb, but not Mb. If the supernatant is clear, the pigment is Hb. If the supernatant is red, the pigment is Mb. Alternatively, Hb can be detected using spectrophotometry and Mb by an electrochemiluminescence immunoassay.

Hematuria is defined as 2–5 RBCs per HPF on microscopic urinalysis. This amount of blood in the urine can be detected using the urine dipstick test. Intermittent hematuria is not uncommon and may occur as a result of exercise or mild to moderate exertion. Persistent (2–5 RBCs per HPF on 2/more urinalyses), significant (>100 RBCs per HPF on single urinalysis), or gross (macroscopic) hematuria must be promptly evaluated for a pathological cause. Hematuria can be microscopic or macroscopic.[3]

Hematuria is one of the common reasons for cystoscopic examinations to rule out malignancy in elderly patients. The indications for further urological evaluation in patients with microscopic hematuria have been well-studied but continue to be debated. Mariani et al evaluated the risk-benefit and cost-effectiveness of urological evaluation in 1000 patients with asymptomatic microscopic and gross hematuria between 1976 and 1985.[3] In this population, 88.3% of the patients had a lesion that could explain hematuria and 9.1% had life-threatening lesions. The incidence of life-threatening lesions was higher in elderly (>50) and male subjects. A total of 18.6% of patients with life-threatening lesions had at least one urinalysis with less than 3 RBCs per HPF within 6 months of diagnosis. The study concluded, in terms of risk-benefit and cost-effectiveness, microscopic or gross asymptomatic hematuria was a significant finding and warranted evaluation.[4]

Further studies have questioned the use of microscopic hematuria as a sole indicator for ruling out malignancy. A retrospective analysis of 156,691 patients with hematuria suggested that low grade hematuria (<25 RBC/HPF) was not a reliable indicator of malignancy (with a 3-year incidence of urological malignancy of only 0.43%).[5]

In a subsequent prospective cohort study of 2630 patients with microscopic hematuria, the overall cancer detection rate was only 1.9%. In this study gross

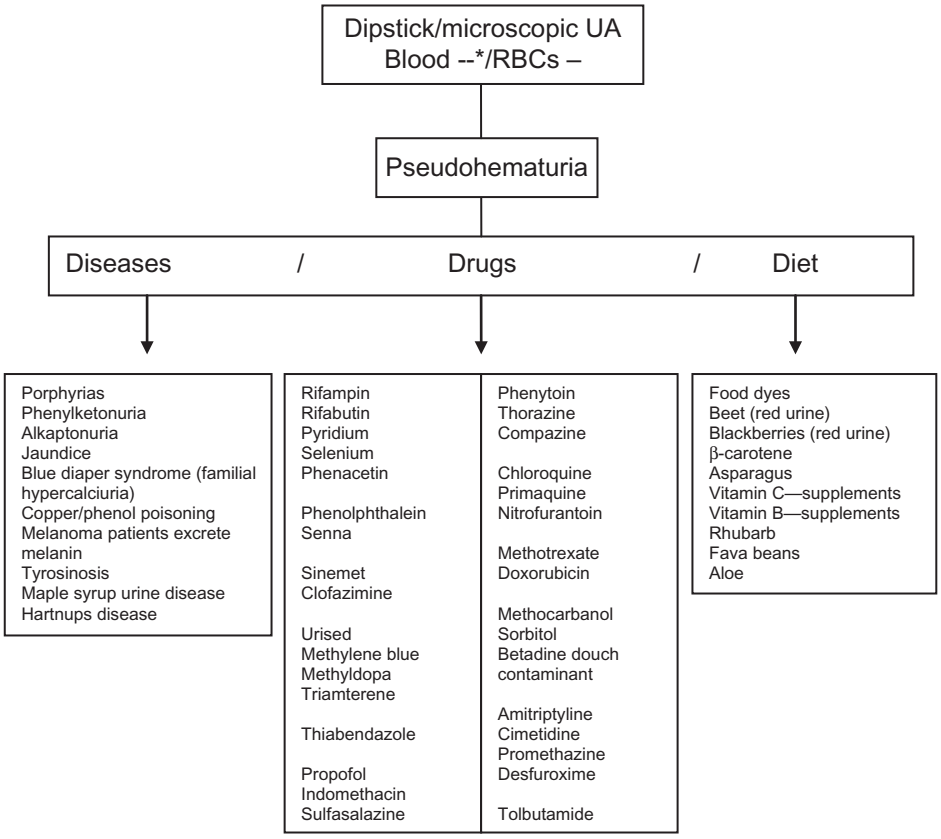

Figure 4. Pseudohematuria.
Note: *Dipstick is usually negative for blood. However, there may be rare situations when it may be weakly positive for blood.

hematuria was found to be a stronger indicator of malignancy.[6]

The American Urological Association recommends further urological evaluation (starting with a cystoscopy) in patients with any of the following: smoking, occupational exposure to chemicals or dyes, gross hematuria, age > 35 years, previous urologic disease, history of irritative voiding symptoms, and history of recurrent urinary tract infection despite appropriate use of antibiotics. In contrast, initial evaluation for primary renal disease is recommended for patient with microscopic hematuria along with any of the following: significant proteinuria (defined as >500 mg of protein per day), dysmorphic red blood cells, red blood cell casts in urine, and elevated serum creatinine level.[7–9]

Paroxysmal Nocturnal Hemoglobinuria

History

Over the last two centuries, PNH has evolved into a clinical syndrome.[10–12] In 1866, Sir William Gull first described hematinuria in a young anemic patient. This was recognized as Hb in urine by Paul Strübing, a German physician, in 1882. He first hypothesized the nocturnal paroxysms of hemoglobinuria as a consequence of erythrocyte lysis secondary to systemic acidosis from CO_2 accumulation during sleep. In 1911, the condition was further described by two Italian physicians, Ettore Marchiafava and Alessio Nazari. In the same year, Hijmans-van den Berg, a Dutch physician, first described that red cells from these patients lysed in acidified serum. The name PNH was coined by Enneking in 1928. The condition was further described by Ettore Marchiafava (1928) and Ferdinando Micheli (1931). In early part of the 20th century, PNH was known by various eponyms (particularly in Europe), including Strübing-Marchiafava-Micheli Syndrome, Marchiafava-Nazari-Micheli Syndrome, or and Marchiafava-Micheli Syndrome.[10–12]

Pathophysiology and clinical manifestations

PNH is an uncommon acquired clonal disorder characterized by paroxysms of intravascular hemolysis. It is the result of an acquired somatic mutation of the

phosphatidylinositol glycan class A (PIG-A) gene on the X-chromosome of a hematopoietic stem cell.[13,14] The PIG-A gene is necessary for the biosynthesis of glycosylphosphatidylionositol anchor proteins (GPI-AP) which help attach a number of proteins to the external surface membrane of RBCs. Approximately 20 such proteins are absent from the red cell membranes of patients with PNH. Two of these, CD55 [also known as decay accelerating factor (DAF)] and CD59 [also known as membrane inhibitor of reactive lysis (MIRL) or membrane attack complex inhibitor factor (MACIF)],[15,16,20,21] have been implicated in the clinical manifestations of PNH. CD55 and CD59 help block complement activation on the cell surface of RBCs. The absence of these proteins thus accounts for the increased susceptibility of red cells to complement lysis. Similar mechanism accounts for increased tendency of platelets to abnormally initiate clotting.[17–21]

Primary clinical manifestations of PNH include hemolytic anemia, bone marrow failure, and venous thrombosis.

Bone marrow failure problems such as aplastic anemia, myelodysplastic syndromes and myeloproliferative disorders have been shown to be associated with PNH.[22]

Hemolytic anemia in PNH patients is due to complement-mediated intravascular hemolysis. Coombs' test is negative in these cases. Intravascular hemolysis produces anemia, hemoglobinuria, elevated LDH, elevated reticulocyte count, indirect hyperbilirubinemia, and low haptoglobulin. Chronic loss of Hb in urine leads to iron-deficiency anemia. In a series of 80 patients with PNH studied by Dacie and Lewis, 35 patients presented with symptoms of anemia, 26 with hemoglobinuria, 18 with hemorrhagic signs and symptoms, 13 with aplastic anemia, 10 with gastrointestinal symptoms, 9 with hemolytic anemia and jaundice, 6 with iron-deficiency anemia or thromboembolism, 5 with infections, and 4 with neurologic signs and symptoms.[23]

Intravascular hemolysis is a pathognomic feature of PNH. Red cell lysis releases Hb into the plasma, where it binds to haptoglobin (hence the low or undetectable levels of haptoglobin.) Once the haptoglobin-binding capacity of plasma is exceeded, free Hb can be detected in the plasma. Free Hb circulates as a tetramer, ultimately breaking down into dimers. The Hb dimers are filtered through the glomerular membrane in kidney. In the proximal tubules, Hb is reabsorbed and catabolized into heme iron and attached to the storage proteins ferritin and hemosiderin. Hemosiderin can spill into the urine and can be detected by the Prussian blue reaction. Once the reabsorptive capacity of proximal tubules is exceeded, Hb is excreted into the urine, which is known as hemoglobinuria[17] (Fig. 5). Hemoglobinuria can be intermittent and is a clonal disorder. The bone marrow produces abnormal clones mixed with normal clones of hemopoietic cells. The persistence and severity of signs and symptoms depends on the size of the abnormal clones (Fig. 5).

Venous thrombosis is another clinical manifestation of PNH. In PNH patients, somatic mutations also lead to GPI-anchor protein deficient granulocytes and reticulocytes.[24–27] GPI-AP deficient platelets are susceptible to complement-mediated damage to the cell surface, thereby increasing the risk of thrombosis. The risk of thrombosis appears to be directly related to the size of the PNH clone (number of PNH cells in blood). In a review of 163 PNH patients, the 10-year risk of thrombosis in patients with large PNH clones (PNH granulocytes >50%) was 44% compared to 5.8% in those with smaller PNH clones (with PNH granulocytes <50%).[28] Characteristic venous thrombosis at unusual sites, including hepatic, portal, cerebral, mesenteric, dermal veins, observed in PNH is a predictor of morbidity and mortality for these patients.

Rother and Hillmen et al studied the role of nitric oxide depletion in clinical manifestations of PNH.[29] This is based on a theory by Schechter et al describing the role of nitric oxide in the vascular system.[30] Nitric oxide participates in vasodilation and vascular hemostasis. Rother and Hillmen described the role of excess free Hb as a scavenger of nitric oxide by converting it to nitrate. They also described the action of erythrocyte arginase (released from red cell lysis) in decreasing nitric oxide synthesis by degrading the substrate L-arginine.[29] Manifestations of nitric oxide depletion on smooth muscle tone and platelet activation/aggregation include pulmonary and systemic hypertension, erectile dysfunction, dysphagia, and intravascular thrombosis (Fig. 5).

Because of the variations in presenting features, clinical manifestations, and natural history, classifica-

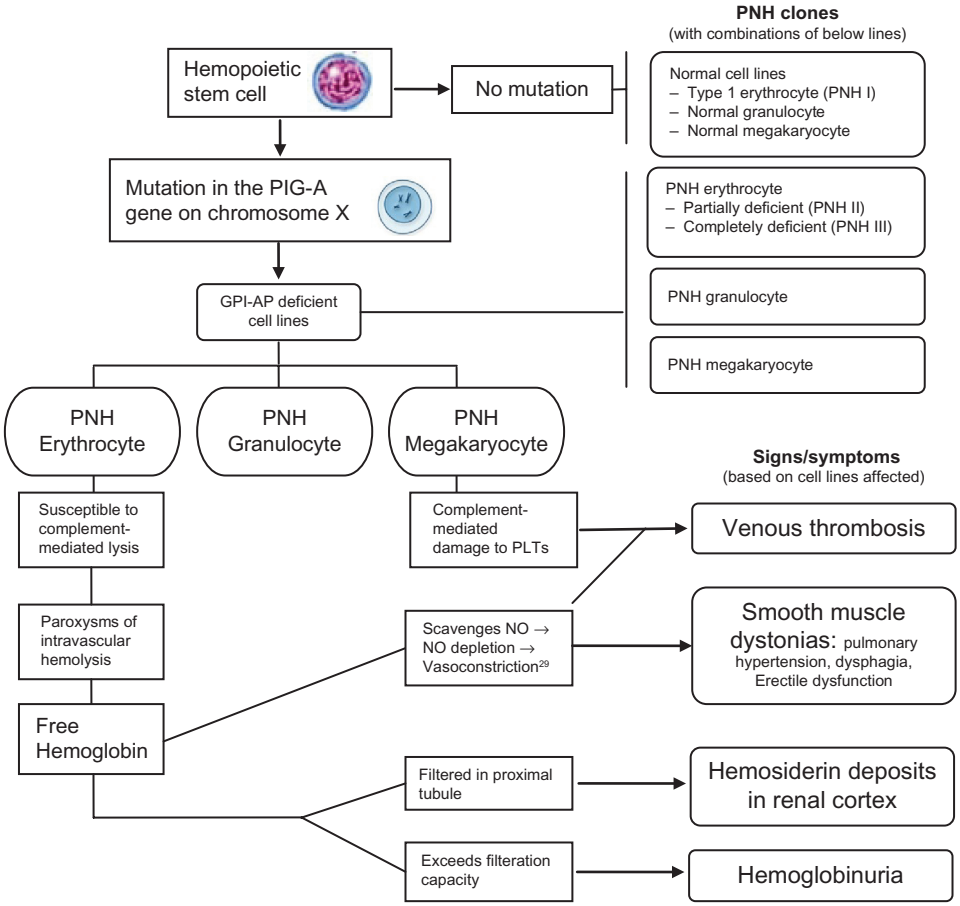

Figure 5. Pathogenesis and clinical manifestations of PNH.
Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria; PIG-A gene, Phatidylinositol glycan class A gene; PLTs, Platelets; NO, Nitric oxide; GPI-AP, Glycosylphosphatidylionositol anchor proteins.

tion of PNH into three sub-categories was proposed by Parker et al in 2005.[31]

- Classic PNH.
- PNH in setting of another bone marrow disorder, including PNH/aplastic anemia or PNH/refractory anemia-MDS.
- Subclinical PNH (PNH-sc) in setting of another bone marrow disorder, for example, PNH-sc/aplastic anemia.

Recommendations were made by Parker et al in 2005 to the International PNH Interest Group regarding screening for PNH.[31] Patients with one or more of the following presentations are good candidates for PNH screening:

- Patients with hemoglobinuria.
- Patients with iron-deficiency anemia and Coombs'-negative intravascular hemolysis.
- Patients with venous thrombosis involving unusual sites (hepatic, portal, mesenteric, cerebral, or dermal veins).
- Patients with aplastic anemia.
- Patients with refractory anemia-MDS.
- Patients with episodic dysphagia or abdominal pain on a background of intravascular hemolysis.

The peripheral blood may contain distinct clones of PNH cells within the same patient. In other words, a normal set of erythrocytes can be mixed with abnormal erythrocytes. Phenotypic expression of cells varies based on the degree of mutation. Three CD59-defined red cell populations include PNH Type 1 (normal), PNH Type II (partial deficiency of CD59), and PNH Type III (complete deficiency of CD59) (Fig. 5). Partial expression of CD55 and CD59 on PNH type II cells may be sufficient enough for preventing in vivo hemolysis.

Diagnostic approach

A stepwise approach is used for diagnosing suspected PNH. Step 1: Confirm hemoglobinuria. Step 2: Document iron deficiency anemia. Step 3: Look for intravascular hemolysis—elevated LDH, reticulocyte count, and indirect bilirubin; and low haptoglobin. Step 4: Serologic tests and flow cytometry. Step 5: MRI of kidneys, liver and spleen to look for hemosiderin deposition.

Serologic tests

Detect complement-mediated hemolysis

a. Sucrose lysis test (eponym—sugar lysis test).
b. Hams test (eponyms—acid serum test, acidified serum test, or Ham-Dacie test).
c. Complement lysis sensitivity test (CLS).[32]

The sucrose lysis test was described in the 1970s. A patient's RBCs are placed in low ionic strength solution (10% sucrose) and observed for hemolysis. It is a sensitive test in patients with PNH and sometimes used as a screening test for PNH, but the specificity is low (results may be positive in other hemolytic anemias such as autoimmune hemolytic anemia). A more specific test, Ham's test, was first described by Thomas Hale Ham in 1937, when he showed the lysis of PNH red cells in acidified serum.[4] Low ionic strength solution and acidified serum activate complement-mediated cell lysis. The specificity of Ham's test is good; however, a positive result is also observed in congenital dyserythropoietic anemia. The complement lysis sensitivity test (CLS) is not commonly used.

Flow cytometry

Detect missing GPI-anchor proteins.

a. Single color analysis: flow cytometry immunophenotypic analysis to detect GPI-APs (CD55 and CD59) on peripheral blood smear (erythrocytes, granulocytes, lymphocytes, or platelets).
b. Two-color analysis: a modified version of the above, except that fluorescent-labeled monoclonal antibody cell markers against the GPI anchor proteins (anti-CD55, anti-CD59) are used along with flow cytometry immunophenotyping.[33]

Flow cytometry using monoclonal antibodies (anti-CD55 for erythrocytes; anti-CD55 and anti-CD59 for granulocytes) was found to be more sensitive and specific and yielded quantitative analysis compared to serological tests for detecting complement-mediated hemolysis.[33] Erythrocytes with partial expression of GPI-APs are more readily identified using anti-CD59 than anti-CD55. GPI-AP-deficient granulocytes can also be identified using anti-CD16. GPI-AP-deficient lymphocytes can be identified using monoclonal antibodies to CD55, CD59, and CD48. Because of the longevity of lymphocytes (compared to other cell lines), GPI-AP-deficient lymphocytes can be detected in PNH patients even after the disappearance of abnormal erythrocytes and granulocytes (seen in patients undergoing disease remission).[33,34]

Imaging studies

PNH is a chronic disorder. Prolonged filtration of hemoglobin through the kidneys results in hemosiderin deposits in the cells of proximal tubules in the renal cortex. T1- and T2-weighted MRI of kidneys showed decreased signal intensity in the renal cortex compared to in the renal medulla.[35–37] Similar findings of decreased signal intensity in spleen and liver have been reported.[36] It is thought to be secondary to either transfusion-associated hemosiderosis or a possible result of hepatic or portal vein thrombosis. Upon computed tomography scanning of the kidneys (without contrast), the attenuation of the renal cortices is higher than the renal medulla with hemosiderin deposition.[35]

Management

Blood transfusions maintain Hb levels and correct iron deficiency anemia. Androgens and glucocorticoids have been shown to reduce the rate of hemolysis.

Advances in therapy are focused on pathogenesis of hemolysis. CD55 and CD59 proteins on the cell surfaces block complement activation. Loss of these proteins makes the blood cells susceptible to hemolysis. Hillmen et al studied the role of eculizumab, a synthetic monoclonal antibody, for managing PNH.[38] Eculizumab inhibits the terminal complement system and has shown to decrease the rates of hemolysis (measured as decreased LDH levels), increase the proportion of PNH type III cells (reflecting the increased survival of these cells), decrease transfusion requirements, and improve the quality of life by reducing symptoms (hemoglobinuria and dysphagia).

A one-year study also showed good safety and tolerability of eculizumab.[38–40]

Venous thrombosis is a complication of PNH. Acute thrombosis, for example Budd-Chiari syndrome or cerebral thrombosis, are treated with thrombolytic therapy. After an episode of thrombosis, these patients are typically placed on long-term anticoagulation with warfarin. However, role of prophylactic anticoagulation for preventing thrombosis in PNH has been controversial because of the high risk of bleeding in these patients.

Conclusions

A step-wise approach to a patient with discolored urine can lead to expedited diagnosis of the etiology and help with timely management. This article also gives a comprehensive overview of a rare but commonly missed diagnosis of PNH as a cause of discolored urine.

Author Contributions

Conceived and designed the experiments: PVR. Analyzed the data: PVR. Wrote the first draft of the manuscript: PVR. Contributed to the writing of the manuscript: PVR. Agree with manuscript results and conclusions: PVR. Jointly developed the structure and arguments for the paper: PVR. Made critical revisions and approved final version: PVR. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author discloses no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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