



Case Reports

Unprovoked Venous Thromboembolism in a Patient with a Small PNH Clone: A Therapeutic Dilemma

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder commonly presenting with hemolytic anemia and thrombosis. Treatment of acute thrombotic events usually involves a combination of complement inhibitor therapy and anticoagulation. We report the case of a 69-year-old female with history of PNH in spontaneous remission who presented nearly two decades later with unprovoked venous thromboembolism (VTE). Flow cytometry detected a small PNH without evidence of hemolysis, creating a dilemma regarding the need for complement inhibitor therapy. She was ultimately treated with anticoagulation alone. This case highlights the unknown aspects of the natural history of PNH and the challenges in managing venous thromboembolism in patients with persistent small PNH clones.

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by uncontrolled complement-mediated intravascular hemolysis of affected red blood cells, leading to clinical manifestations such as anemia, thrombosis, and smooth muscle dystonias.¹ An interesting aspect in the natural history of this condition that has been well described is the possibility of spontaneous remission with the disappearance of PNH clones.² The availability of flow cytometry has enabled the detection of small PNH clones that would otherwise have been missed by the outdated Ham's test, which relied on the lysis of PNH red cells in an acidic environment.¹ The clinical significance of small PNH clones in the absence of active hemolysis is unknown.

CASE PRESENTATION

A 69-year-old female patient presented to her primary care physician with two weeks of bilateral lower extremity swelling, a dry cough with one episode of blood-tinged sputum production, and left-sided posterolateral chest pain. She was prescribed amoxicillin-clavulanate and azithromycin for suspected pneumonia. She was also noted to be tachycardic, and a CT pulmonary angiogram was done due to concerns of pulmonary embolism. The scan showed bilateral pulmonary emboli, more pronounced on the right, and a saddle component at the pul-

monary artery bifurcation. She was sent to the emergency department for further management.

Laboratory testing revealed a hemoglobin of 14.4 g/dL, a white cell count of 7,500/ μ L, and a platelet count of 275,000/ μ L. Coagulation studies showed an INR of 1.1 and an APTT of 30.1 seconds. Fibrinogen was 548 mg/dL, and the D dimer level was >7650 FEUng/mL. Renal and liver function tests were normal. Total bilirubin was 0.5 mg/dL, LDH was 329 U/L, haptoglobin was 252 mg/dL, and reticulocyte count was $62.8 \times 10^9/L$ (1.5%). Anti-cardiolipin and beta-2 glycoprotein antibodies were within normal limits. A peripheral smear did not reveal any significant morphological abnormalities. Direct Coombs test was negative. Iron studies showed iron of 29 ug/dL, iron saturation of 10%, and TIBC of 282 ug/dL. Urinalysis was positive for moderate blood, but no RBC were seen on microscopy. Repeat CT chest showed interval resolution of saddle embolus with otherwise similar bilateral clot burden distribution with evidence of right heart strain. A transthoracic echocardiogram showed a D-shaped interventricular septum in diastole, consistent with right-sided volume overload. Doppler ultrasound of the lower extremities revealed an acute right-sided deep vein thrombosis extending from the calf veins into the femoral vein up to the level of the common femoral vein, and an acute left-sided deep vein thrombosis involving the posterior tibial and peroneal calf veins.

She had a past medical history of immune thrombocytopenia (ITP), for which she was initially treated with

steroids and later underwent splenectomy in her 20s without subsequent recurrence. In her 30s, she was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) after presenting with multiple blood clots, including Budd-Chiari syndrome, along with dark urine. She was treated with warfarin for over a decade, after which it was discontinued because the patient no longer had evidence of active hemolysis, and her PNH was considered to be in remission. She did not have any recent prolonged travel, immobilization, surgeries, hospitalizations, or new medications. She does not smoke cigarettes. She had a recent upper respiratory tract infection a few weeks prior. She was up to date with age-appropriate cancer screening, including colonoscopy and mammography. She denied any alcohol or recreational drug use. She also denied any family history of blood clots, hematologic disorders, or malignancies.

She was initially treated with an intravenous heparin infusion, which was later transitioned to enoxaparin. Interventional radiology did not recommend thrombolysis. Hematology was consulted for her remote history of PNH. Flow cytometry of peripheral blood revealed that 2.39% of red blood cells exhibited loss of CD59, while 0.04% of monocytes and 0.75% of granulocytes were of the PNH clone. Given that the laboratory workup showed no evidence of hemolysis, the unclear significance of her small PNH clone, and the cost of complement inhibitor therapy, the decision was made not to initiate complement inhibition. She was transitioned to apixaban and discharged home with outpatient follow-up. During follow up appointment two weeks post-discharge, her leg swelling persisted, but her breathing and chest pain had improved. She was planned for indefinite anticoagulation with apixaban and regular follow-up with the hematology clinic to monitor hemolysis parameters and PNH clone size, to guide future need for complement inhibitor therapy.

DISCUSSION

Paroxysmal nocturnal hemoglobinuria (PNH) develops from a somatic mutation in an X-linked gene named phosphatidylinositol glycan class A (PIGA), which mediates the first step of glycosylphosphatidylinositol (GPI)-anchor biosynthesis. This results in a deficiency of the GPI-anchored complement regulatory proteins CD55 and CD59 on red blood cells (RBCs).¹ Absence of CD55 leads to uninhibited C3 convertase activity on erythrocytes, leading to the formation of the membrane attack complex (MAC).¹ Absence of CD59 permits unchecked MAC formation, resulting in uncontrolled complement activation and subsequent intravascular hemolysis of GPI-deficient RBCs.¹ Diagnosis of PNH requires deficiency or absence of GPI-anchored proteins in 2 more lineages on peripheral blood flow cytometry.¹ Clinico-pathologically, PNH is classified into three groups: 1)

Classical PNH characterized by intravascular hemolysis and risk of thrombosis, associated with greatest benefit from complement inhibition; 2) PNH in the context of other primary bone marrow disorders, most commonly aplastic anemia; and 3) Subclinical PNH with small PNH clones without clinical or laboratory evidence of hemolysis, and for which complement inhibition has no role.³ The most widely accepted treatments for PNH include terminal complement inhibition and allogeneic bone marrow transplantation.¹

Venous thrombosis, often in the hepatic vein, is more common than arterial thrombosis.¹ Mechanism of thrombosis is multifactorial, including complement activation of PNH platelets, nitric oxide scavenging by free hemoglobin leading to platelet activation and aggregation, and defective fibrinolysis from deficiency of GPI-linked proteins.¹ Complement inhibition is the most effective means of preventing thrombosis. With their use, the survival rate is comparable to that of age-matched healthy individuals, and thrombosis is no longer associated with increased mortality.³ Management of acute thrombotic events in PNH varies. Some experts recommend overlapping anticoagulation with complement inhibition for 3-6 months, then discontinuing anticoagulation if thrombotic symptoms have resolved and the disease is well controlled with the complement inhibitor.⁴ There is no evidence to support the use of primary prophylactic anticoagulation in PNH.¹

PNH is rare, with an estimated incidence of 1 to 10 per million person-years, and a prevalence of 12 per million, with a median age of onset in the 30s and no clear racial or gender preponderance.³ The condition was first described in 1882 by Dr. Strübing, and the term 'paroxysmal nocturnal hemoglobinuria' was later introduced by Enneking in 1925.¹ Tiny PNH clones may exist in healthy individuals, but a PIGA mutation can give those cells a survival advantage under autoimmune stress, allowing the PNH clone to expand.¹ PNH is associated with other bone marrow disorders.¹ Fatizzo et al. reported about 25% prevalence of PNH clones ranging from <1% to <10% in aplastic anemia and myelodysplastic syndrome (MDS).⁵ A prospective study involving 75 patients with PNH clones could not identify a statistically significant association between clone size and thrombosis or hemolytic markers.⁶

In a study that prospectively followed 80 patients with PNH for up to 48 years, 15 percent of patients had spontaneous remissions between 10 and 20 years after the diagnosis. It has been hypothesized that PNH clones have a limited lifespan and that remission may occur if normal stem cells repopulate the bone marrow.⁷ Another study demonstrated that PIGA clones may be replaced by CHIP (Clonal Hematopoiesis of Indeterminate Potential) like mutations in myeloid genes (such as ASXL1), which can have a greater fitness advantage leading to Dar-

winian selection.² In one other study with 106 Finnish patients with PNH clones, 6 patients had either disappeared or diminished clones, and 2 of them subsequently developed leukemia. However, all 6 patients had underlying aplastic anemia or bone marrow failure.⁸ This potential risk of malignant transformation highlights the importance of continued monitoring of patients with PNH remissions.

Our patient had a recurrent thromboembolic event approximately two decades after spontaneous remission of PNH with no identifiable provoking factors for venous thromboembolism. She was found to have a small PNH clone, however given the absence of hemolysis, complement inhibitor therapy was deferred, and the decision was made to treat with anticoagulation alone. She was planned for indefinite anticoagulation given the unprovoked nature and severity of VTE. It is unclear about the clinical significance of small PNH clones and the natural history of long-standing PNH remissions. Although the literature reports a risk of malignant transformation

with recrudescence of the PNH clone, our patient has no evidence of an underlying stem cell disorder; however, a bone marrow exam was not performed. Further studies are needed to establish the clinical significance of small PNH clones.

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Disclosures/Conflicts of Interest

The authors declare they have no conflicts of interest

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