Case Report: Paroxysmal Nocturnal Hemoglobinuria

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, life-threatening hematopoietic stem cell disorder characterized by the triad of hemolytic anemia, thrombosis, and impaired bone marrow function. PNH arises due to an acquired mutation in the synthesis of the glycosylphosphatidylinositol (GPI) anchor protein, which leads to a deficiency of complement regulatory proteins and unregulated complement-mediated hemolysis.[1] With a reported incidence of 1 to 10 cases per million and a 3-5% risk of developing leukemia, new therapeutic advances have emerged to decrease the 10-year mortality associated with PNH.[2,3] Here, we discuss the presentation of a 59-year-old male with PNH, strategies to diagnose this rare condition, and therapeutic challenges regarding anticoagulation in these patients.

CASE PRESENTATION

The patient is a 59-year-old Russian-speaking male with a past medical history significant for diabetes and hypertension who presented to the Emergency Department (ED) with two days of fever, headache, and altered mental status. The headache was described as a constant, 7/10 bilateral posterior headache that radiated anteriorly and improved with over-the-counter acetaminophen. His family described his altered mental status as confusion regarding recent events and short-term memory loss. The patient denied photophobia or neck stiffness. He denied changes in vision, unilateral weakness, loss of sensation, or any other focal neurological deficits. He had no recent travel or sick contacts. He is a former cigarette smoker (40 pack-year history) and social drinker with no history of illicit drug use.

On admission, the patient was noted to be febrile to 103.1° F, tachycardic to 121 beats per minute, tachypneic to 22 breaths per minute, and normotensive at 121/70. On physical exam, he was awake, alert, and oriented to person, place, and time but not to situation or recent events. He was noted to have scleral icterus and hepatomegaly. The remainder of the physical exam was unremarkable. Labs on admission were notable for anemia (Hemoglobin 7.7, baseline of 9.4), thrombocytopenia (Platelet count of 108, baseline of 152), transaminitis (AST 84, ALT 53), hyperbilirubinemia (Total Bilirubin 1.9, Direct Bilirubin 0.7), and coagulopathy (PT 30.9, PTT 43, INR 3.8). The patient's renal function was within normal limits. A CT scan of his head on initial presentation was unremarkable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for fever, headache, altered mental status, anemia, thrombocytopenia, and indirect hyperbilirubinemia includes both intrinsic and extrinsic causes of hemolysis. Intrinsic hemolytic causes include hemoglobinopathies, hereditary spherocytosis, and paroxysmal nocturnal hemoglobinuria. Extrinsic hemolytic causes include disseminated intravascular coagulation (DIC), antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), autoimmune hemolytic anemia (AIHA), and infections such as malaria and babesiosis.

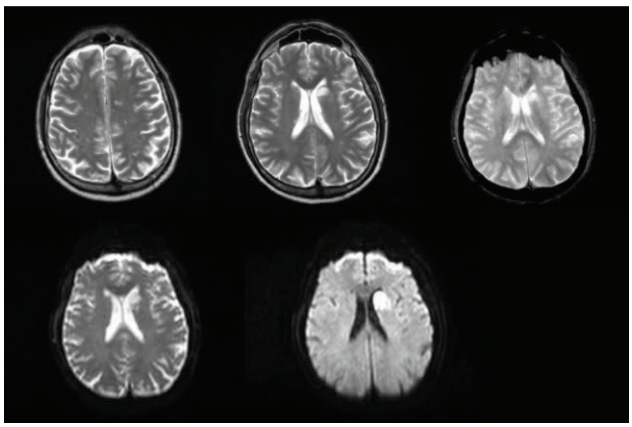

Figure 1. Brain MRI – Day 2 of presentation. The Images demonstrate multiple foci of recent infarction in the supratentorial and tentorial brain; and no evidence of intracranial hemorrhage.

HOSPITAL COURSE

The patient defervesced after Day 2 of his hospitalization. As part of his infectious work-up, blood and urine cultures were sent and demonstrated no growth. His chest x-ray was unremarkable. A lumbar puncture was done in the ED on arrival and was unrevealing with glucose 80, protein 31, and no RBCs or WBCs.

Due to persistent, severe headaches and concern for possible intracranial thrombosis, an MRI of the brain was done and revealed multiple subacute periventricular ischemic emboli bilaterally (Figure 1). MRV of the brain did not show cavernous venous thromboses. MRA of the brain did not show any clots in the Circle of Willis.

Persistent transaminitis and concern for portal vein thrombosis resulted in a Doppler ultrasound of the abdomen which excluded reversal of blood flow. An MRI

of the abdomen revealed splenomegaly with splenic infarcts, renal cortical hemosiderosis, and hepatomegaly with altered perfusion representing hepatic sinusoidal obstruction syndrome (SOS) (Figure 2).

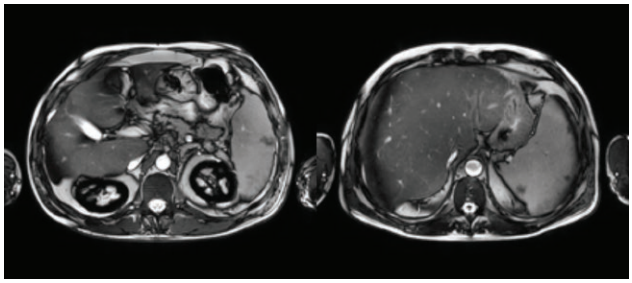

Figure 2. MRI abdomen – Day 2 of persistent transaminitis. The images demonstrate hepatomegaly with altered perfusion and attenuated but patent hepatic vasculature; splenomegaly with splenic infarcts; and renal cortical hemosiderosis, which can be seen with paroxysmal nocturnal hemoglobinuria.

Workup for the cause of the patient's hemolytic anemia included studies for antiphospholipid antibody syndrome, TTP, DIC, HUS, hereditary spherocytosis, and AIHA—all of which were not revealing. The fluorescein-labeled proaerolysin (FLAER) and flow cytometry assay to look for GPI anchor protein and CD55-59 deficient cells, respectively, were performed. The results of the assays were diagnostic of paroxysmal nocturnal hemoglobinuria (Table 1). A bone marrow biopsy was also performed which showed a normocellular bone marrow with trilineage hematopoiesis, relative erythroid hyperplasia and rare stainable iron, and no evidence of abnormal myeloid lymphoid, or plasma cell populations.

Non–Erythroid Cell Type	%
Granulocytes	68%
Lymphocytes	25%
Monocytes	3%
Blasts	0%
Lymphoid Cell Type	**%**
B Cells (CD20+)	9%
T Cells (CD3+)	82%
NK Cells (CD56+/CD3-)	7%
Kappa to Lambda ratio	1.5
CD4 to CD8 ratio	2.0

Table 1. FLAER results and differential count of total non-erythroid cells.

The B-lymphoid cells constitute 9% of all lymphoid cells and are polyclonal for immunoglobulin light chain expression. The T-lymphoid cells constitute 82% of all lymphoid cells and demonstrate a CD4:CD8 ratio of 2:1 Blasts are not detected.

MANAGEMENT AND FOLLOW-UP

The patient was started on unfractionated heparin and bridged to warfarin. On Day 6 of his hospitalization, he began eculizumab, a humanized monoclonal antibody that is a terminal complement inhibitor and the only known FDA-approved treatment for PNH. After two doses of eculizumab, the patient showed significant clinical improvement. His headaches, mental status, hemolysis, and transaminitis all improved. Stem cell transplantation was deemed unnecessary as his blood counts stabilized prior to discharge. He was discharged home on warfarin with the plan to follow-up with hematology-oncology and to continue receiving eculizumab as an outpatient.

A week after discharge, the patient received his third treatment of eculizumab. The patient received the meningococcal vaccination and the pneumococcal vaccination due to elevated risk of infection from encapsulated organisms following eculizumab treatment. Eculizumab predisposes patients to life-threatening *Neisseria meningitides* infections (0.5% per year), meriting both vaccination as well as prophylactic penicillin.[4] The patient will receive lifelong anticoagulation with warfarin (INR goal 2-3). He was scheduled to have repeat imaging of his liver and follow up with hepatology due to his sinusoidal obstruction syndrome.

DISCUSSION

The most common presentation of PNH is fatigue (80%), followed by dyspnea (64%) and hemoglobinuria (62%).[5] Thrombosis is seen in only 16% of cases, yet it represents the most common cause of mortality in PNH. The venous system – especially atypical vessels such as the portal, mesenteric, and hepatic veins – is more commonly affected than is the arterial system, which makes this patient's case atypical.[6] Furthermore, intracerebral sites are less commonly involved than intraabdominal sites.[6] The major risk factors for thrombosis are the proportion of PNH granulocytes (PNH clone size) and the degree of intravascular hemolysis.[5] Europeans have also been shown to be at increased risk for thrombosis when compared to Asian patients.[1] The diagnosis of PNH is confirmed with peripheral blood flow cytometry by detecting the absence of GPI-APs on $\geq$2 lineages with a reagent known as fluorescent aerolysin (FLAER).[4]

Eculizumab is the drug of choice in managing patients with PNH. It must be administered indefinitely for a sustained response. Two multinational phase 3 trials, the TRIUMPH and SHEPHERD trials, concluded that eculizumab is highly effective in stopping intravascular hemolysis, decreasing the need for red cell transfusions with >70% achieving transfusion independence, improving quality of life, and reducing the risk of thrombosis.[7,8] Furthermore, patients on eculizumab and anticoagulation had a lower thromboembolic rate than those on anticoagulation alone.

Severe anemia, thrombosis, renal insufficiency, and dyspnea are all strong indications to initiate therapy. Corticosteroids may improve hemoglobin levels and reduce hemolysis, but their minimal benefit is overshadowed by their long-term toxicity. Allogeneic stem cell transplant is an option for patients with severe aplastic anemia or those who are unresponsive to eculizumab therapy.[4]

An ongoing controversy in PNH is management of thromboses. No consensus exists for primary prophylaxis, given the unpredictability of thromboembolic events. Primary prophylaxis should be used for patients with PNH clones larger than 50% or those with additional genetic risk for thrombosis, including ethnicity. As for secondary prophylaxis, patients experiencing any thromboembolic event should remain on lifelong anticoagulation. However, there is still no consensus in regards to the best strategy for anticoagulation. Both low molecular weight heparin (LMWH) and warfarin at different therapeutic ranges are utilized, with some physicians considering the addition of antiplatelet agents.[1] Oral thrombin inhibitors with a more favorable therapeutic index than warfarin may also be used in patients with PNH.

In this particular case, the most challenging aspect was balancing the need for anticoagulation with the risk of hemorrhagic stroke in a patient at high risk for poor medical literacy and medication non-compliance. After consulting the Neurology service, the non-malignant Hematology service, and the Anticoagulation and Thrombosis service, it was ultimately decided to continue the patient on anticoagulation as the risk for further thrombotic events outweighed the risk of hemorrhagic conversion of the subacute ischemic strokes. It was felt that warfarin, a reversible anticoagulant, would be safer in the short term.

Verbal consent was obtained from the patient to publish this case report.

REFERENCES

1. Rositano AM, Rotoli B. Paroxysmal nocturnal hemoglobinuria: pathophysiology, natural history and treatment options in the era of biological agents. *Biologics : Targets & Therapy.* 2008;2(2):205-222.
2. Melo A, Gorgal-Carvalho R, Amaral J, et al. Clinical management of paroxysmal nocturnal haemoglobinuria in pregnancy: three case reports. *Blood Transfusion.* 2011;9(1):99-103.
3. Mohammed, A.A., EL-Tanni, H., Atiah, T.AM. et al. Paroxysmal Nocturnal Hemoglobinuria: From Bench to Bed. *Indian Journal of Hematology and Blood Transfusion* (2016) 32: 383.
4. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood.* 2014;124(18):2804-2811.
5. Schrezenmeier H, Muus P, Socié G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. *Haematologica.* 2014;99(5):922-929
6. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood.* 2005;106(12):3699-3709.
7. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *New England Journal of Medicine.* 2006; 355: 1233-1243.
8. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood.* 2008; 111: 1840-1847.