A case of classic paroxysmal nocturnal hemoglobinuria

**Krishnamoorthy Seetharaman, Suja Lakshmanan,
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ABSTRACT

Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia characterized by a triad of intravascular hemolysis, pancytopenia and tendency for venous thrombosis. Patients with PNH present with these features which occur in various combinations as described in this case report. Several episodes of intravascular hemolysis result in hemoglobinuria associated with thrombosis at unusual sites and these patients may have varying degree of bone marrow disorders. Diagnosis can be confirmed by flow cytometry of blood granulocytes and FLAER assays. Management was supportive with transfusion and treatment of thrombosis in the past. But in the recent years the evolution of treatment strategies like hemopoietic stem cell transplantation and complement inhibition with eculizumab though very costly have been shown to be very effective.

Case Report: Here we report a young girl who presented with abdominal pain, distension with a history of headache and jaundice. On evaluation, we found there was bicytopenia with evidence for hemolytic anemia and venous thrombosis of cerebral venous sinuses, hepatic veins and intrahepatic portion of IVC. With these clinical features, we suspected paroxysmal nocturnal hemoglobinuria which was later confirmed by flow cytometry.

Conclusion: Having diagnosed her disease, we had to decide on various treatment options like eculizumab, hemopoietic stem cell transplantation which are efficient therapies for PNH. When these modalities are not possible in our case we had to adopt conservative management.

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CASE REPORT

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and venous thrombosis of cerebral venous sinuses, hepatic veins and intrahepatic portion of IVC. With these clinical features, we suspected paroxysmal nocturnal hemoglobinuria which was later confirmed by flow cytometry. **Conclusion:** Having diagnosed her disease, we had to decide on various treatment options like eculizumab, hemopoietic stem cell transplantation which are efficient therapies for PNH. When these modalities are not possible in our case we had to adopt conservative management.

Keywords: Budd–Chiari syndrome, Eculizumab, Multiple venous thrombosis, Paroxysmal nocturnal hemoglobinuria (PNH)

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemopoietic disorder which is a rarity in occurrence. Available reports suggest that the incidence of clinically significant disease 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 is in thirties [1]. Though PNH is caused by mutation of a gene on X chromosome it affects males and females equally [2]. This disease is classified under acquired hemolytic anemia with constellation of certain clinical findings. They present with clinical features of unexplained hemolytic anemia like fatigue, jaundice and red colored urine. Thrombosis involves

venous rather than arterial system and the presentation depends upon the site of thrombosis like hepatic, portal, mesenteric and cerebral veins. The delay in the diagnosis of this disease may be either because of the disease being rare or due to nonspecific clinical features. Prompt and accurate diagnosis is important as effective therapies have become available. This has become very much possible because diagnostic testing has evolved significantly due to the better understanding of the molecular basis of the disease and eventually the pathogenesis of hemolysis in PNH. We present a 21-year-old female with combination of symptoms and signs that made us to diagnose this rare disorder and also we have discussed the difficulties in the management of this patient.

CASE REPORT

A 21-year-old female presented with complaints of jaundice for one month; fever abdominal pain and distension for 15 days. She was admitted in an outside hospital with complaints of left sided headache, blurring of vision in the right eye for one day with no history of any significant illness in the last or chronic drug intake. Her menstrual cycles have been irregular for the last two years. She had a younger brother who is healthy. There she was found to have anemia with thrombocytopenia. MRI scan of BRAIN revealed left parietal and occipital hemorrhages (Figure 1). Workup for connective tissue diseases like ANA, dS-DNA and APLA were done and found to be negative. Bone marrow biopsy was done and revealed hypercellular marrow with no other abnormality.

As they were unable to pin point the crux of the problem, she was referred to our institution for persistent fever, abdominal pain and distension with persistent headache. On examination she was afebrile, pulse rate 80/min, blood pressure 110/70 mmHg, marked pallor was present. Cardiovascular and respiratory examination were normal. Her abdomen was soft with minimal distension and diffuse tenderness. She also had hepatomegaly which was 3 cm below the right costal margin and presence of shifting dullness. Her CNS examination revealed no focal neurological deficits. Fundus Examination showed few superficial hemorrhages in the retina of right eye with visual acuity 6/6.

Initial laboratory tests (Table 1) revealed reduced hemoglobin, low platelets, raised LDH, slightly elevated bilirubin along with transaminases (AST>ALT), negative direct coombs test and inconclusive marrow. Urine had grown *Enterococcus faecalis*.

Ultrasonography (USG) of abdomen showed thrombosis involving intrahepatic segment of Inferior vena cava and hepatic confluence. There was also hepatomegaly with coarse echotexture with ascites. Since thrombosis was made out we worked her up for thrombotic states. Homocysteine level was normal. ANA, Antiphospholipid antibody, Anti cardiolipin anti body and lupus anticoagulant were negative. Then we proceeded

Table 1: Laboratory investigation of the patient.

Hemoglobin	5.2 g/dL%
Total count	5900
Differential count	Polymorph 64, Lymphocyte 27, Monocyte 7, Basophil 0.6, Eosinophil 0.4
Platelets	1.3 lakhs/mm ³
Peripheral Smear	Normocytic normochromic RBCs, Adequate platelets, MP,MF: Negative
Mean corpuscular volume	91.9 fL
Mean corpuscular hemoglobin	28.6 pg
Mean corpuscular hemoglobin concentration	31.1
Erythrocyte sedimentation rate	55 mm/hr
Serum Iron	94 mg/dl
Serum ferritin	67.50 ng/dl
Total iron binding capacity	463
Prothrombin time	14.1
Partial thromboplastin time	41.1
International normalized ratio	1.34
Lactate Dehydrogenase	1849 U
T. BILIRUBIN	1.5 mg/dl
Aspartate aminotransferase	202 U/L
Alanine aminotransferase	135 U/L
Urea & creatinine	Normal
Thyroid profile	Normal
Stool Occult blood	Negative
Direct Coomb's Test	Negative
Viral markers(HBsAg, anti HCV, HIV)	Negative
Urine routine examination	Albumin 1+, hemoglobin +
Blood culture	No growth
Urine culture	Enterococcus faecalis (colony count 10 ⁵)
Bone marrow	Reactive marrow, Megaloblastic maturation with binucleate forms, All stage of maturation with giant metamyelocyte

with CECT scan of abdomen which was consistent with USG abdomen and was suggestive of Budd–Chiari syndrome (Figure 2A–B).

In order to know the cause of persistent headache, we did MRI scan of brain with venogram which showed sub acute hemorrhage of size 3.5x2.5 cm in left occipital lobe and absent flow was noted in left transverse, sigmoid sinuses and upper jugular vein (Figure 3) suggestive of cerebral venous thrombosis. Later ophthalmologists

Figure 1: Magnetic resonance imaging scan of brain showing multiple areas of hemorrhages in left lobe of cerebellum, parietal and occipital lobes.

Figure 2: (A, B) Computed tomography scan of abdomen-Intra hepatic portion of inferior vena cava showing thrombosis as shown in circle.

Figure 3: Thrombosis involving left transverse sinus, sigmoid sinus and upper jugular vein.

suspected branched retinal vein occlusion and advised fluorescein angiogram but patient was not willing for the procedure.

Our patient had hemolysis as evidenced by raised LDH, thrombosis at multiple sites (IVC, cerebral venous sinuses and possibly retinal vein) and bicytopenia-anemia and thrombocytopenia. This triad of features made us to suspect PNH. In order to confirm the same, we did flow cytometry which showed evidence of PNH clone upon analysis of granulocytes and monocytes [CD 59--47% NEG (>20% NEG in granulocytes) and CD 55--56.7% NEG].

With the classical triad of features and a positive flow cytometry final diagnosis of paroxysmal nocturnal hemoglobinuria was made. Hematologist opinion was sought and patient was started on LMWH, enoxaparin 60 mg subcutaneous twice daily for five days overlapped with oral anticoagulant, acenocoumarol 4 mg which was continued. She was also given three units of packed cell transfusions and appropriate antibiotics for UTI.

As a definitive therapy her brother was worked up for allogeneic hemopoietic stem cell transplantation. HLA typing was done initially which didn't match with the patient. Hence we could not proceed further with bone marrow transplantation. Other option was eculizumab C5 complement antagonist which was unaffordable by the patient. Patient's hemoglobin and platelet count improved by then and she was discharged with acenocoumarol 4 mg daily, later adjusted according to PT, INR, folic acid 2 mg daily and ferrous fumarate 300 mg twice daily.

On subsequent follow-up patient used to complaint of abdominal distension and pain on and off. Hemogram showed well preserved hemoglobin, leukocyte and platelet counts. Repeat USG abdomen showed the persistence of thrombosis in hepatic vein and intra hepatic portion of inferior vena cava and ascites. When patient has been followed up for almost two years we found that she had persistent hepatic vein thrombosis and developed features of cirrhosis; but she did not develop thrombosis at any other sites.

DISCUSSION

We report a young girl who presented with headache, abdominal pain and distension with past history of jaundice was found to have bicytopenia and venous thrombosis at multiple sites. Diagnosis of PNH was confirmed by typical clinical features and flow cytometry.

In PNH there is complement induced lysis of RBCs due to the abnormal sensitivity of RBC cell membrane. This is due to an acquired defect in the gene for phosphatidylinositol class A (PIG A) thereby causing deficiency of glycosylphosphatidylinositol (GPI) which is sheet anchor for cell membrane proteins [3]. CD55 and CD59, complement regulatory proteins which block intravascular and extravascular hemolysis respectively in normal human, are deficient in PNH [4]. Hemolysis

occurs in PNH because these patient's RBC's lack GPI anchor which is required to attach CD55 and CD59 to the surface of RBC [4]. This permits unregulated formation of certain complement attack complex which damages RBC membrane resulting in intravascular hemolysis. This causes reduction in hemoglobin and hemoglobinuria with resultant increase in LDH [3]. Next feature is thrombosis which is the leading cause of death in patients with PNH [4]. The pathogenesis causing thrombosis is not completely understood; but hypothesized to be due to free hemoglobin resulting from hemolysis attracts nitric oxide which induces vasoconstriction and damages the vascular endothelium forming a nidus for thrombus formation. Also platelets release procoagulant particles during complement induced hemolysis, which facilitate thrombosis. Thromboses involve the venous rather than the arterial system [4]. Venous thrombosis often occurs in locations such as hepatic, portal, mesenteric, dermal, and cerebral veins [5]. Minority of patients develop pancytopenia due to bone marrow disorders like aplastic anemia or primary myelofibrosis.

PNH is classified into classic PNH (presence of hemolysis with no marrow abnormality), PNH with marrow disorders (aplastic anemia/myelodysplastic syndrome (MDS)/primary myelofibrosis (PMF) and subclinical PNH—without clinical evidence [6]. Before making the final diagnosis of PNH, we have to rule out other hemolytic anemias like autoimmune anemias, hereditary anemias, drugs/toxin induced anemias, microangiopathic hemolytic anemias and bone marrow disorders like aplastic anemias, MDS and myelofibrosis. Abdominal or cerebral vein thrombosis due to PNH must be differentiated from other hyper coagulable states and thrombophilias. The diagnosis of PNH can be suspected when we come across cases of coombs negative hemolytic anemia or confusing cases of pancytopenia.

The established therapies for patients with classical PNH are allogeneic hematopoietic cell transplantation (HCT) and complement inhibition with eculizumab [3]. Patients with hemolysis are better managed with eculizumab [7]. Patients with thrombosis are managed with therapeutic anticoagulation and eculizumab. Most of the patients will not be able to access this therapy due to its high cost. Allogeneic HCT is advised for patients with severe cytopenias, patients with poor response to eculizumab or when not accessible to eculizumab [3]. Supportive therapy includes red blood cell (RBC) transfusions, supplemental iron and folic acid (1 to 2 mg daily).

Our patient had features of classical PNH—bicytopenia, hemolysis and venous thrombosis at three sites intraabdominal cerebral and retinal with no marrow involvement. We learn that it is difficult to diagnose this disease unless we have a high index of suspicion. We present this case due to its rarity and the difficulties we had in diagnosing and the management when both bone marrow transplant and eculizumab were not feasible.

CONCLUSION

In this presentation, a young girl who presented to us with bicytopenia and hemorrhagic cerebral infarct with recent history of jaundice was found to have coombs negative hemolytic anemia and multiple venous thrombosis (hepatic, cerebral, retinal). It has always been said that in a case of confusing cases of hemolytic anemia and pancytopenia, we must suspect paroxysmal nocturnal hemoglobinuria (PNH); more so when it is coupled with venous thrombosis. Having diagnosed PNH, the management recommended is very costly and should be affordable for the patient.

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Author Contributions

Krishnamoorthy Seetharaman – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article and Final approval of the version to be published

Suja Lakshmanan – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the article and Final approval of the version to be published

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Giridhar Muthu – Acquisition of data, Analysis and interpretation of data, Critical revision of the article and Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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SUGGESTED READING

- Medicine up-to-date, Harrison's principles of internal medicine, CMDT-2014, Davidson's principles and practice of medicine.

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