Successful outcome of Pregnancy in an adolescent female with Aplastic Anemia-PNH on Eculizumab- A case report.

Preethi Reddy Marri, MD; Guy Grayson, MD; Arlynn Mulne, MD,

Department of Pediatrics, Hematology-Oncology, The Children’s Hospital at Scott and White, Texas A&M University of Health Sciences, Temple, Texas.

Resident Research Day-03/25/2010
INTRODUCTION

- Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare acquired chronic clonal stem cell disorder characterized by
  1. Paroxysmal intravascular hemolytic episodes,
  2. Hemoglobinuria,
  3. Thrombocytopenia and
  4. Thrombotic tendencies as a result of complement mediated intravascular hemolysis.

PNH frequently arises in association with disorders of bone marrow failure, particularly Aplastic Anemia.

- In women with PNH, anemia from hemolysis, underlying bone marrow failure or both frequently worsens during pregnancy.

- Thrombotic events are the leading causes of morbidity and mortality in pregnant patients with PNH, associated with an increased risk of complications for both mother and fetus.
PNH – Triad of Clinical Features

Intravascular Hemolysis

Thrombosis

Bone Marrow Failure

Associated symptoms

Anemia
Abdominal pain
Headache
Dysphagia
Erectile failure
Severe fatigue

Venous
Liver (Budd Chiari)
Abdominal-
(Hemosiderin deposition)
Cerebral Arterial

Aplastic Anemia/MDS
Precedes/coexists with PNH
CASE PRESENTATION

August 2000-Initial Presentation

- Eight year old Caucasian female presented to ED at Scott and White hospital with stomach pain and non bilious, non bloody vomiting for about 2 weeks. Review of systems was negative. But she was pale appearing with ecchymotic areas on both shins and spinous processes.

- Labs revealed marked pancytopenia (WBC: 2100/mcL, Hemoglobin: 3.5 gm/dL, Hematocrit: 9.9 %, Platelets: 6000/mcL, MCV: 110.6 fL)

- Bone marrow aspiration and biopsy revealed Aplastic Anemia. The hematopoietic tissue is almost completely replaced by fat.

- 2 courses of Immunosuppressive therapy with Prednisone, Cyclosporine and Antithymocyte Globulin done which was tolerated well. She was continued on daily cyclosporine as well and tapered in November 2005.
Figure 1: Bone marrow section from the patient at initial presentation reveals Aplastic Anemia. Compared to normal marrow, Hematopoietic cells are almost totally absent. Sinuses and capillaries are prominent.
Counts stabilized and she was followed in the clinic as needed.

Cytogenetic studies revealed 46, XX : normal female karyotype.

Regular bone marrow examinations showed hypoplastic marrow but no significant dysplastic changes either by light microscopy, cytogenetics or FISH. Pancytopenia reoccurred in 2007.

She was evaluated at Cook Children’s hospital in Fort Worth, Texas for evaluation of matched unrelated Bone Marrow transplantation in 2007.
Presented to ED with severe periumbilical abdominal pain and Hemoglobin of 6.0 gm/dL and Hematocrit of 18.9%. LDH was elevated to 5000 U/L.

MRA/MRV abdominal/pelvis revealed Hemosiderin deposition in Renal cortices but no thrombus was detected.

Flow cytometry of Bone marrow aspiration and biopsy confirmed 99% PNH clone. 50% of red blood cells had either partial or complete CD59 deficiency. The Monocytes had 88% CD14 deficiency, and Granulocytes had 92% CD24 deficiency.

Meningococcal vaccine given and followed up in the clinic. Started on Soliris per protocol.
Evaluation of the intraabdominal organs: demonstrates hypo intense T2 weighted signal bilaterally within the Renal cortices, Liver and Spleen consistent with Hemosiderin deposition.

Normal T2 weighted Abdominal MRI images for comparison. Note that the Signal intensity is uniform in the Liver, Spleen and in Renal cortices unlike the index case.
Flow Cytometric analysis shows a Significant PNH Clone (greater than 1% GPI-deficient cells) within the RBC’S, Granulocytes and Monocytes. These findings are consistent with a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH).
The induction phase refers to once a week dose for the first 4 weeks and Maintenance phase refers to 1.5 times the initial dose on week 5 and once every 2 weeks thereafter.

![Dosing schedule](image-url)
CASE PRESENTATION

- LDH significantly dropped from within 10 days of therapy, required fewer transfusions and much improved fatigue.

- Headache was a significant complaint but well managed with Tylenol.

May 2009

- She was found to be Pregnant and subsequently referred to Obstetrics department for management of high risk pregnancy and close monitoring.

- Soliris regimen was continued with regular monitoring of LDH and CBC’s. She had adequate Neutrophil count, platelets were stable around 50,000/mcL and anticoagulation could not be initiated. Required multiple transfusions to keep Hemoglobin above 9 gm/dL. No thrombotic complications during pregnancy.

- She delivered a live, healthy female infant at 37 weeks gestation by spontaneous vaginal delivery without complications.
Variation in LDH levels with/without intervention

- LDH peak around PNH diagnosis
- Rise in LDH with inappropriate treatment
- Fall in LDH with Soliris
DISCUSSION

The symptoms of PNH include hemoglobinuria, intravascular hemolysis, thrombosis, and thrombocytopenia. Presentation can be as:

A. Classical PNH- no bone marrow suppression
B. PNH-in the setting of another specified bone marrow disorder (e.g. PNH/Aplastic anemia or PNH/refractory anemia-MDS)²

Paroxysmal Nocturnal Hemoglobinuria has been described as a clonal disease. The development of PNH clone is thought to require two coincident factors: 1. Somatic mutation of the PIG-A gene in one or more cells,
2. Abnormal bone marrow environment.

Progeny of affected stem cells are deficient in Glycosyl Phosphatidyl Inositol-Anchored Proteins (GPI-AP), CD55 and CD59 accounting for the intravascular hemolysis. Flow cytometry of granulocytes shows evidence of an expanded PNH clone in a large proportion of marrow failure patients, including aplastic anemia patients, even in the phase of recovery.
Disorder characterized by a defect in the GPI Anchor due to an abnormality in the PIG-A gene.
Flow cytometric analysis using antibodies directed against GPI-AP is the most sensitive and informative assay available for diagnosis of PNH.

The FLAER (Fluorescently labeled Aerolysin) assay takes advantage of binding of a bacterial protein, aerolysin, to GPI-AP.

Acidified serum lysis test (Ham’s test) and the sucrose lysis test (sugar water test) are both less sensitive and less quantitative than flow cytometry.
Thrombo-embolism is a serious and life-threatening complication in PNH with a well established predilection for the hepatic veins. The mechanism of thrombosis is thought to be:

1. Free hemoglobin causes Nitric Oxide scavenging by platelets
2. The generation of procoagulant platelet micro vesicles due to the absence of the terminal complement inhibitor CD59, and the interaction of red cell micro vesicles and soluble urokinase plasminogen activator receptor.

Anticoagulation is commonly used in patients with PNH with thrombosis, but may be limited by thrombocytopenia.
Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5, which results in inhibition of complement-mediated cell lysis. Recommended for patients with disabling fatigue, thromboses, transfusion dependence, frequent pain paroxysms, renal insufficiency or other end-organ complications from disease. --Improves quality of life!

Most patients notice symptomatic improvement within hours to days after the first dose. Treatment needs monitoring with CBC, reticulocyte count, LDH and biochemical profile.

Prospective analysis of patient data pooled from 3 clinical studies and a common extension study revealed that Eculizumab treatment resulted in dramatic reduction in the Thrombo-Embolic event rate from 7.37 to 1.07 events per 100 patient-years.

Of the side effects reported, Headache was most common and well managed with Tylenol before the infusion of Soliris.
Complement Inhibition in PNH

Classical
Lectin

C3b
CD55

C5
C5a
C6 C7 C8 C9
CD59

Alternative

MAC
C5b-9

Normal

PNH

C5 inhibiting antibody

Bessler Blood 2005
Bone Marrow Transplant is the only potentially curative therapy for PNH and associated thrombophilia but is limited by lack of suitable donors and associated with significant morbidity and mortality.

女性PNH患者通常被劝阻怀孕，因为有10%的风险发生严重血栓-栓塞性事件，伴有高死亡率和其他并发症如感染、出血、贫血和增加的流产、胎儿死亡和早产风险。

管理团队应包括有经验的血液科医生和专门处理高风险妊娠的妇产科医生，根据需要提供血液制品治疗贫血和血小板减少症。孕妇PNH患者的额外需要补充叶酸和铁。建议使用低分子量肝素抗凝，除非有禁忌症。尽管存在许多担忧，成功结果似乎是常态。然而，需要进一步经验与Eculizumab的安全性在怀孕中进行评估6。
CONCLUSION

- Eculizumab is the only Food and Drug Administration–approved drug for the treatment of PNH. Eculizumab reduces intravascular hemolysis, thrombotic events and improves quality of life in patients with PNH. But:
  1. Expensive
  2. PNH clone not eradicated
  3. Life long treatment

Best reserved for:
  1. Symptomatic patient with large PNH clone
  2. Presence of thrombosis irrespective of the PNH clone size.

- There were no congenital anomalies, birth defects and no thromboses reported in recent studies with Eculizumab. Our case report further supports this conclusion.

- The influence of Eculizumab on stem cell transplant is yet to be studied.
FUTURE DIRECTIONS

There is a worldwide patient registry begun in 2004 in order to generate more detailed epidemiologic data and gain greater insight into the disease and the outcomes of therapy.

Gene therapy remains a promising possibility, although a greater understanding of pathophysiology of PNH is required as well as advances in gene therapy techniques.
REFERENCES


7. Dahl-Chase Diagnostic services, Department of pathology, Bangor, Maine.
SPECIAL THANKS TO

DR. ARLYNN MULNE MD, DR. GUY GRAYSON MD

AND

DR. JOSE SANTIAGO MD.