Paroxysmal Nocturnal Hemoglobinuria

35 yr. female 15 weeks pregnant with her second child presents to ER with abdominal pain that is in both upper quadrants although R > L. Pain has been persistent for several days prior to ER visit
She denies nausea or vomiting although her appetite has been less for the past few days
No fever or change in bowel habits
Felling well until pain started several days prior to presentation
PMH is negative, no meds except prenatal vitamins
Prior pregnancy uneventful, vaginal delivery of a healthy son 2.5 years ago

Paroxysmal Nocturnal Hemoglobinuria: A Chronic Disabling and Life-Threatening Disease

- Estimated 4,000 – 6,000 patients in U.S.
- 5 year mortality: 35%
- Diagnosed at all Ages – Median age early 30’s
- Quality of life diminished
- Progressive disease

![Graph showing actuarial survival from the time of diagnosis](image)
Design of Complement

- Originally thought to be 1 protein, but now known to be at least 27 proteins
- Initiation phase
- Localization on membrane surfaces
- Activation and amplification—from inactive to active (3 pathways)
- Regulation—control and return to inactive state
- Function—disruption of membrane

Regulators of Complement Activation

Absence of CD59 Allows Terminal Complement Complex Formation
Multimeric C9 lesions on PNH erythrocyte membrane

Genes of PNH
A Somatic Mutation in the PIG-A Gene in 1 HSC

GPI-linked proteins deficient on a clone of blood cells

Selection of defective HSC

Expansion of defective clone

PNH and aplastic anemia

HSC = hematopoietic stem cell.

Paroxysmal Nocturnal Hemoglobinuria

- It's not paroxysmal
  - Even in the absence of symptoms, destructive progression of hemolysis is ongoing
- It's not nocturnal
  - Hemolysis in PNH is subtle and constant, 24 hours a day
- Hemoglobinuria is a less commonly seen complication
  - ¾ patients present without hemoglobinuria

Consequences of Chronic Hemolysis and Free Hemoglobin

Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors

Without this protective complement inhibitor shield, PNH red blood cells are destroyed

Complement Activation

Intact RBC

Thrombosis
Renal Failure
Pulmonary Hypertension
Abdominal Pain
Dyspnea
Fatigue
Hemoglobinuria
Erectile Dysfunction

Significant Impact on Survival

Fatigue
Dyspnea
Dysphagia
Hemoglobinuria
Erectile Dysfunction

Significant Impact on Morbidity

Free Hgb/Anemia

Common Symptoms in Patients With PNH

- 41% Dysphagia
- 47% Pulmonary Hypertension
- 66% Dyspnea
- 57% Abdominal Pain
- 64% Chronic Renal Insufficiency
- 47% Erectile dysfunction
- 26% Hemoglobinuria
- 40% Thrombosis
- 89% Anemia
- 96% Fatigue, Impaired QoL
Thrombosis in PNH: 
Common and Frequent Cause of Death

- 40% of patients with clinical thrombotic events
- Leading cause of death
  - Accounts for 40–67% of deaths
  - First thrombotic event can be fatal
  - Median time to TE was 2.1–2.3 years from diagnosis
  - First TE increases risk for death 5 to 10-fold

Mechanisms for Thrombosis in PNH

Multifactorial pathogenesis of thrombosis in PNH:
- Hemolysis
  - Reduced Nitric Oxide
  - Platelet hyperreactivity
  - Hypercoagulability
  - Prothrombotic membranes
- Excessive platelet activation from CD59 deficiency
- Impaired fibrinolysis, receptor for urokinase-type plasminogen activator (u-PA) is deficient on PNH leukocytes
- Platelet consumption may result from microthrombi
- Endothelial cell perturbation
  - Tissue factor initiated coagulation independent of hemolysis
  - C5a
  - Elevated inflammatory/coagulation markers including D-dimer

Evidence of Thrombosis in Never–Transfused PNH Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median LDH (n=34)</td>
<td>1,360 U/L</td>
</tr>
<tr>
<td>Evidence of Thromboembolism (n=43)</td>
<td>28%</td>
</tr>
<tr>
<td>TE events per 100 patient years</td>
<td>7.85</td>
</tr>
<tr>
<td>TE rate in patients with PNH clone ≤50% (n=8)</td>
<td>33%</td>
</tr>
<tr>
<td>TE rate in patients with PNH clone &gt;50% (n=24)</td>
<td>30%</td>
</tr>
</tbody>
</table>

15% of this patient cohort had LDH levels <500 U/L, indicating PNH patients with low levels of hemolysis are at risk for thrombosis

*Uncontrolled observational case series, AU, IT, FR, NL, US
Never transfused PNH
PNH Can Be Challenging to Diagnose

Delays in diagnosis range from 1 to more than 10 years.

Directly question patients for all potential symptoms

<table>
<thead>
<tr>
<th>Clinical Signs or Symptoms</th>
<th>Incidence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>86%</td>
</tr>
<tr>
<td>Chronic Renal Insufficiency</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>96%</td>
</tr>
<tr>
<td>Hemoglobinuria (at presentation)</td>
<td>26%</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>41%</td>
</tr>
</tbody>
</table>

Delays in diagnosis range from 1 to more than 10 years.

Directly question patients for all potential symptoms


Flow Cytometry performed on peripheral blood

More than one cell lineage should be evaluated

- Granulocytes
- Monocytes
- Red Blood Cells (RBC)

Quantitative Results

- Sensitivity Level ≥0.01%
- Easy to understand PNH Reports
- Use monoclonal antibodies against GPI-anchored proteins, such as CD14, 24, 59 and FLAER


Standard Diagnostic Test for PNH

- Flow Cytometry performed on peripheral blood
- More than one cell lineage should be evaluated
  - Granulocytes
  - Monocytes
  - Red Blood Cells (RBC)
- Quantitative Results
  - Sensitivity Level ≥0.01%
- Easy to understand PNH Reports
- Use monoclonal antibodies against GPI-anchored proteins, such as CD14, 24, 59 and FLAER

Flow Cytometry for PNH
**Types of PNH Cells**

- Type I Erythrocytes—NORMAL RED BLOOD CELLS with normal levels of CD59 and CD55 on surface
- Type II Erythrocyte has a partial lack of CD59 and/or CD55
- Type III Erythrocyte has total lack of CD55 and CD59

**Why Look Beyond RBCs for PNH?**

- Percentages of PNH RBCs may be affected by:
  - Hemolysis
  - Blood Transfusion
- Granulocytes provide more accurate representation of PNH clone size
- PNH reports should provide quantitative results expressing clone size on both granulocytes and erythrocytes

**Clinical Manifestations of PNH based on Cell Types**
Historical Management of PNH

- Transfusions
  - Risk of iron overload
  - Transient treatment of anemia
- Anticoagulants
  - Risk of hemorrhage
  - Ineffective in many patients
- Red cell supplements
  - ESAs may expand clones and elevate hemolysis
  - Folic acid, iron, erythropoiesis–stimulating agents
- Steroids/androgen hormones
  - No controlled clinical trials
  - AE’s

Anticoagulants

- Risk of hemorrhage
- Ineffective in many patients

Historical Management of PNH

Bone Marrow Transplant

- BMT is associated with significant morbidity and mortality
- Hemolysis and thrombosis are risk factors for poor outcomes
- In a recent retrospective study in France examining PNH patients: 1
  - 54% had GVHD
- In another study examining PNH patients (n=23): 2
  - 50% chronic GVHD; 42% acute GVHD
- BMT has a significant impact on quality of life post transplant: 3,4
- Allogeneic BMT recommended for PNH patients with life-threatening cytopenias or possibly the rare patient with disabling hemolysis or thrombosis not controlled with existing therapy: 5

- De Latour PF et al. Abstract #316. EBMT 2009; 2
- Santarone S et al. Hematogica. 2009; 3
- Bieri S et al. BMT. 2008; 4
- Fraser CJ et al. Blood. 2006; 5
- Brodsky RA. Blood. 2009 113: 6522-6527

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Treatment Of PNH

Management of PNH based on disease classification

- Compass PNH based on flow cytometry characteristics, hematology trait score, serum LDH concentration, bone marrow analysis
- Reduced PNH
- PNH/BMP syndrome
- Classic PNH

- No specific PNH therapy—focus on underlying BMP genotype
- Focus on BMPs
  - Patients with large BMP clones may benefit from treatment
  - Treatment with eculizumab

- Eculizumab, reduced/elimination, or investigational care

- Consider for patients with chronic allogeneic stem cell transplantation

- BMT is associated with significant morbidity and mortality

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SOLIRIS® Blocks Terminal Complement

- SOLIRIS® binds with high affinity to C5
- Terminal complement – C5a and C5b-9 activity blocked
- Proximal functions of complement remain intact
- Weak anaphylatoxin
- Immune complex clearance
- Microbial opsonization

Summary of Clinical Efficacy

In clinical trials, SOLIRIS® significantly reduced hemolysis¹ the underlying cause of morbidity and mortality in PNH

- 86% sustained reduction in hemolysis as measured by LDH²
- Fewer thrombotic events were observed with SOLIRIS in clinical trials¹,³
  ◦ The majority of patients (63%) received concomitant anticoagulant therapy¹
  ◦ The effect of anticoagulant withdrawal during SOLIRIS treatment has not been studied¹
- 78% clinically meaningful improvement in fatigue
- Fatigue in PNH impacted by hemolysis
- Significant improvement noted in pain and dyspnea along with a broad range of QoL measures⁴
- 73% reduction in need for transfusions across all patient populations²

Paroxysmal Nocturnal Hemoglobinuria
Post Eculizumab Survival

Kelly et al. ASH 2010; abstract 639.
**92% Reduction in Thrombotic Events**

- **N=195**

- 63% of patients received concomitant anticoagulants
- The effect of anticoagulant withdrawal was not studied
- Events observed in both venous and arterial sites

**PI:** There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment.


**Pre-Soliris Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Soliris Treatment</th>
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</thead>
<tbody>
<tr>
<td>PP&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Soliris Reduced Thrombosis in Patients Treated with Anticoagulants**

- Pre-Soliris event rate elevated despite use of anticoagulants
- 94% reduction in event rate with Soliris
- Withdrawal of AC has not been studied in patients with PNH

**PI:** There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment.


**Soliris Results in Sustained Improvement Across Broad Range of Measures**

- Large Impact
- Moderate Impact
- Small Impact

**PI:** There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment.

PNH
Key Labs

- CBC with attention to hemoglobin and hematocrit
- LDH
- Reticulocyte count
- Serum creatinine
- BUN
- Bilirubin

Common Symptoms of Hemolysis
Signal the Underlying Threat of Catastrophic Consequences

- Fatigue
- Impaired QoL
- Dyspnea
- Dysphagia
- Abdominal Pain
- Hemoglobinuria
- Erectile Dysfunction
- Anemia
- Chronic Kidney Disease
- Acute Renal Failure
- Pulmonary Hypertension
- Cardiac Dysfunction
- Stroke / TIA
- Ischemic Bowel
- Hepatic Failure