THE UNIVERSITY OF KANSAS CANCER CENTER

Paroxysmal Nocturnal Hemoglobinuria

Barry Skikne MD, FACP, FCP(SA)
Professor of Hematology
Division of Hematologic Malignancies and Cellular Therapeutics

Cardinal Clinical Manifestations PNH

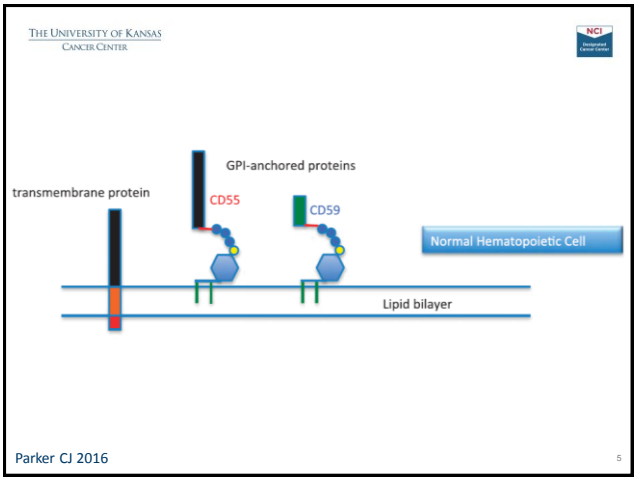
- **Clonal disease but not a malignant disease**
  - transformation to acute leukemia rare
- **Complement mediated intravascular hemolysis**
- **Bone marrow failure**
- **Thrombophilia**

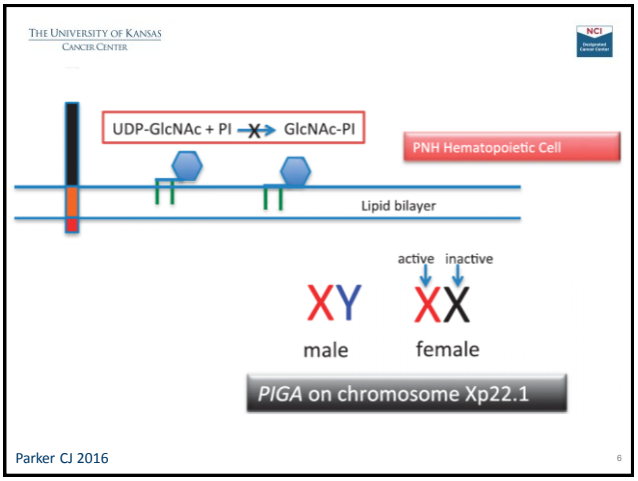
Background - PNH

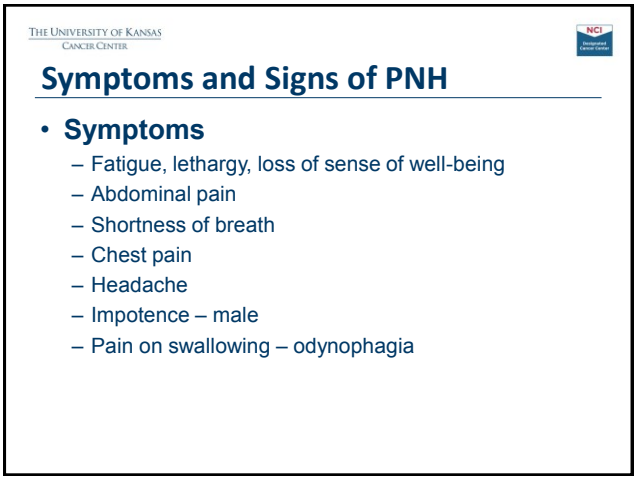
- **Clonal disease involves hematopoietic stem cells**
- **Acquired defect (somatic mutation) – rather than inherited**
- **Mutation of gene (PIGA)**
  - protein product is a glycosyl transferase
  - essential component of synthetic pathway that generates
- **Glycosyl phosphatidylinositol anchor protein (GPI)**
- **PNH cells deficient in GPI**
- **Not confined to red blood cells**

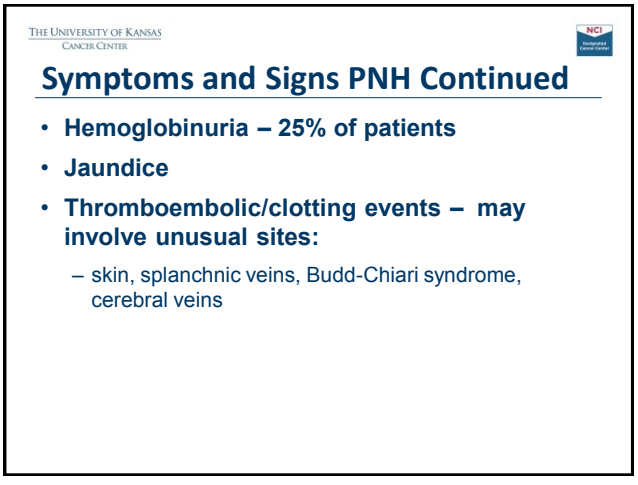
Background - PNH

- **Loss of enzyme function – partial or total**
- **Effects 2 complement inhibitory proteins:**
  - **CD55 (decay accelerating factor[DAF]**
  - **CD59 (membrane inhibitor of reactive lysis [MIRL])**
- **Deficiency of these 2 proteins underlies complement mediated intravascular hemolysis**


THE UNIVERSITY OF KANSAS CANCER CENTER
NCI
transmembrane protein
GPI-anchored proteins
CD55
CD59
Normal Hematopoietic Cell
Lipid bilayer
Parker CJ 2016
5


THE UNIVERSITY OF KANSAS CANCER CENTER
NCI
UDP-GlcNAc + PI
GlcNAc-PI
PNH Hematopoietic Cell
Lipid bilayer
active
inactive
XY
XX
male
female
PIGA on chromosome Xp22.1
Parker CJ 2016
6


THE UNIVERSITY OF KANSAS CANCER CENTER
NCI
Symptoms and Signs of PNH
• Symptoms
– Fatigue, lethargy, loss of sense of well-being
– Abdominal pain
– Shortness of breath
– Chest pain
– Headache
– Impotence – male
– Pain on swallowing – odynophagia


THE UNIVERSITY OF KANSAS CANCER CENTER
NCI
Symptoms and Signs PNH Continued
• Hemoglobinuria – 25% of patients
• Jaundice
• Thromboembolic/clotting events – may involve unusual sites:
– skin, splanchnic veins, Budd-Chiari syndrome, cerebral veins

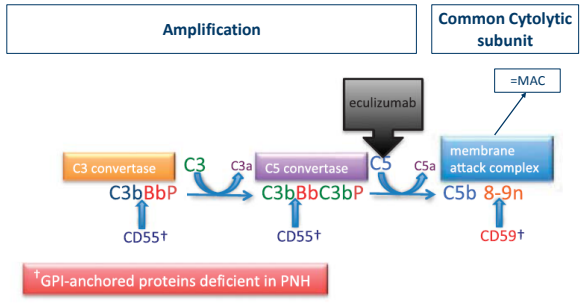
THE UNIVERSITY OF KANSAS CANCER CENTER

Incidence of Clinical Features - PNH

- 97% - Fatigue
- 88% - Anemia
- 66% - Shortness of breath
- 64% - Chronic kidney disease
- 57% - Abdominal pain
- 47% - Pulmonary hypertension
- 47% - Erectile dysfunction
- 41% - Dysphagia
- 40% - Thrombosis
- 25% - Hemoglobinuria

THE UNIVERSITY OF KANSAS CANCER CENTER

Alternate Complement Pathway

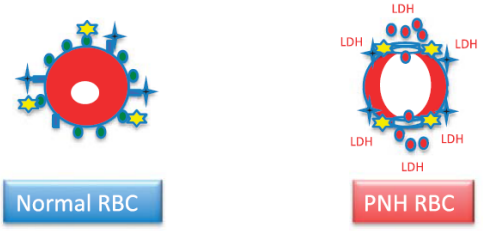


Parker CJ 2016

10

THE UNIVERSITY OF KANSAS CANCER CENTER

Complement-Mediated Hemolysis



Parker CJ 2016

11

THE UNIVERSITY OF KANSAS CANCER CENTER

Classic PNH

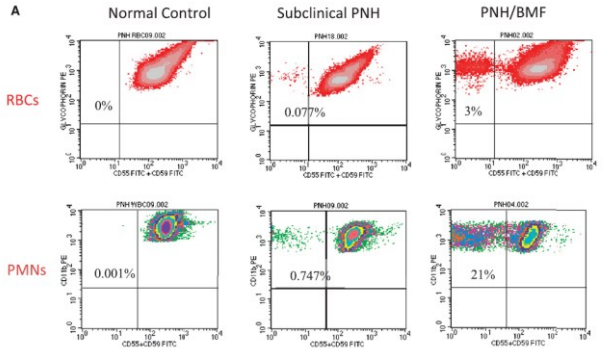
- Have large PNH clone (>50%)
- Have florid intravascular hemolysis – markedly elevated LDH
- Episodic hemoglobinuria
- Experience ongoing constitutional symptoms – lethargy, malaise, asthenia – debilitating
- MAC consists of C5b, C6,C7,C8 and multiple molecules of C9
- If block formation of MAC, can inhibit complement-mediated intravascular hemolysis

THE UNIVERSITY OF KANSAS CANCER CENTER

Laboratory Evaluation

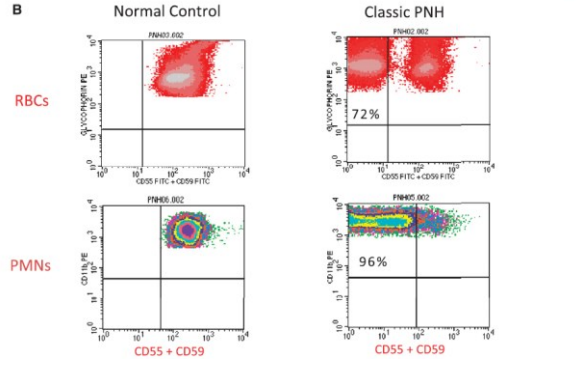
- **Initial:**
  - CBC, blood smear, reticulocyte count
  - Comprehensive chemistry including LDH
  - Other work-up of hemolytic anemias -DATs etc
  - Bone Marrow with cytogenetics, NextGen Sequencing?
- **Diagnosis:**
  - Flow cytometry for CD55 and CD59
- **Ancillary:**
  - Iron studies
  - D-Dimer

THE UNIVERSITY OF KANSAS CANCER CENTER



Parker CJ 2016

THE UNIVERSITY OF KANSAS CANCER CENTER



Parker CJ 2016

THE UNIVERSITY OF KANSAS CANCER CENTER

Eculizumab

- **Humanized monoclonal antibody – binds C5**
- **Preventing C5 activation to C5b by C5 convertase**
- **Thereby inhibits MAC formation**
- **For treatment of hemolysis of PNH**
- **Reduces transfusion requirements – 50%-65% achieve transfusion independce**
- **Ameliorates anemia**
- **Improves quality of life**
- **Serum LDH levels return to normal/near normal**

  But mild/moderate hemolysis, reticulocytosis, Increased bilirubin persist

Treatment - Eculizumab

- **Has no effect on stem cell abnormality or associated bone marrow failure**
- **Leukopenia, thrombocytopenia and reticulocytopenia persist**
- **Treatment must continue indefinitely**
- **May have favorable impact on survival**
- **Risk of meningococcal infections – vaccinate prior to start of therapy**
- **Question of need for prophylactic antibiotics**
- **Dose: 900 mg every 14 days**
- **Can see breakthrough intravascular hemolysis**
  - reduce interval between doses; possibly increase dose

PNH Classification

Category	Intravascular hemolysis rate	Bone marrow	Flow cytometry features	Eculizimab benefit
Classic	Florid – raised LDH Episodic macroscopic Hb-uria	Cellular d/t erythroid hyperplasia, normal or near normal morphology	>50% PMNs GPI-AP deficient	yes
PNH in setting of other marrow failure syndrome	Mild – often minimal markers of hemolysis	Concurrent evidence of marrow failure syndrome	Variable - GPI-AP deficient PMNs usually small <50%	No - but if large clone with significant hemolysis, may benefit
Subclinical	No clinical/biochemical evidence of hemolysis	Evidence of a marrow failure syndrome	Small <10% GPI-AP deficient PMNs	no

Treatment - General

- **All patients have element of marrow failure**
- **If fail to respond/remain anemic**
  - check iron stores and serum erythropoietin level
- **Hemolysis may be mediated by other mechanisms – extravascular hemolysis**
  - opsonization of PNH RBCs by degradation products of C3
  - direct antiglobulin test +ve for C3 (50%) but not IGG
  - may not need treatment – depends on clinical features
  - corticosteroids, splenectomy may ameliorate hemolysis

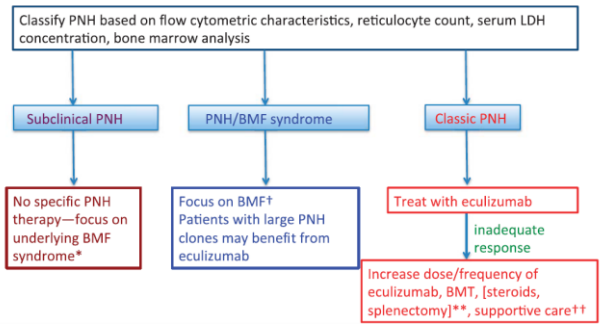
Eculizumab – Soliris Dosing

600 mg IV over 35 minutes every 7 days x 4 weeks
then
900 mg for 5th dose 7 days later
then
900 mg every 14 days thereafter

- **Must vaccinate against meningococcal bacteria at least 2 weeks prior to start of Soliris**
- **Side Effects: headache, back pain, nasopharyngitis, nausea**

THE UNIVERSITY OF KANSAS CANCER CENTER

Management of PNH Based on Disease Classification



Parker CJ 2016

21

THE UNIVERSITY OF KANSAS CANCER CENTER

Questions

22