🩸 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

PNH is an acquired clonal stem cell disorder characterized by complement-mediated intravascular hemolysis, cytopenias, and thrombosis ⚠️

🧬 Etiology & Genetic Basis

- Caused by acquired mutation in PIGA gene
- PIGA → required for synthesis of phosphatidylinositol glycan (PIG) anchor
- PIGA gene is X-linked
- Only one active PIGA gene in hematopoietic cells
  ➜ mutation alone is sufficient ❗

🧪 Cells Affected

- Mutation occurs in an early hematopoietic progenitor cell
- Affects:
  - 🔴 Red blood cells
  - ⚪ Leukocytes
  - 🟣 Platelets

➡ Produces a clonal population of abnormal blood cells

⚙️ PATHOGENESIS

Normal State ✅

- PIG anchor attaches protective proteins to membrane
- Important complement regulators:
  - CD55 (DAF)
  - CD59 (MAC inhibitor)

In PNH — Stepwise Flowchart 🔁

PIGA mutation → ↓ PIG anchor synthesis → Loss of CD55 & CD59 → Red cell membrane unprotected → Excessive complement activation → C5b-C9 membrane attack complex 🧨 → Intravascular hemolysis

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🔴 Why RBCs Are Most Affected

- Leukocytes & platelets also lack protection
- BUT:
  - RBCs are most sensitive to complement lysis
  - Leukocytes are relatively resistant

➡ Hemolysis mainly affects RBCs

🌙 Why "Nocturnal" Hemoglobinuria?

Mechanism Flowchart

Sleep 😴 → Hypoventilation → CO_2 retention → ↓ Blood pH (mild acidosis) → ↑ Complement fixation → ↑

Night-time hemolysis → Morning hemoglobinuria (dark urine) 🚽🩸

🩺 CLINICAL FEATURES

Hemolysis-Related

- Chronic intravascular hemolysis
- Fatigue 😮‍💨
- Pallor
- Hemoglobinuria
- Hemosiderinuria
- Iron deficiency (due to urinary iron loss)

🦴 Bone Marrow Failure Association

- PNH often associated with:
  - Aplastic anemia
- Relationship:
  - Aplastic anemia may precede or follow PNH

- Exact mechanism unclear 🤷‍♂️
- Likely immune-mediated marrow injury

🧱 Thrombosis — Most Dangerous Complication ⚠️

- Major cause of death in PNH
- Occurs in unusual venous sites:
  - Portal vein
  - Hepatic vein (Budd-Chiari syndrome)
  - Mesenteric veins

Thrombosis Pathogenesis

Complement overactivation → Platelet activation → Endothelial injury → Hypercoagulable state → Venous thrombosis

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🧪 LAB FINDINGS

- Features of intravascular hemolysis:
  - ↓ Haptoglobin
  - ↑ LDH
  - Hemoglobinemia
  - Hemoglobinuria
- Progressive iron deficiency

💊 TREATMENT — ECULIZUMAB

Mechanism of Action

Eculizumab → Anti-C5 monoclonal antibody 🎯 → Blocks C5b-C9 MAC formation → ↓ Intravascular hemolysis → ↓ Thrombosis risk 👍

⚠️ Important Limitation

- Does NOT block early complement activation
- C3b still deposits on RBCs
- Leads to ongoing extravascular hemolysis

🦠 Infection Risk with Therapy

C5 inhibition → Loss of terminal complement → ↓ Defense against encapsulated bacteria → ↑ Risk of Neisseria infections (esp. meningococcus)

✅ Mandatory Before Treatment

- Vaccination against Neisseria meningitidis 💉
- Absolutely essential before eculizumab

📌 Exam Summary

PIGA mutation 🧬 → Loss of PIG-anchored complement inhibitors → Complement-mediated intravascular hemolysis → Hemoglobinuria + iron deficiency → High thrombosis risk → Treated with eculizumab (anti-C5)

-> The End <-