A 32-Year-Old Woman with Headache, Abdominal Pain, Anemia, and Thrombocytopenia

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Presentation of Case -- Patient History

- 32-year-old woman
- Lived in coastal New England and worked in communications
- Drank alcohol occasionally
- Smoked less than 1 pack of cigarettes per week, but not in the past few months
- She had taken oral contraception in the past for extended periods of time
- No drugs, over-the-counter medications or herbal medications
4 Weeks Before Admission

- Usual state of health
- Underwent elective termination of pregnancy with methotrexate
- Pregnancy occurred despite of an intrauterine device
- Device removed, oral contraception initiated
1 Week Before Admission

- Pain in the left upper quadrant
- Vaginal bleeding
- Headache developed
- Admitted to another hospital
Lab Results

- Blood level of human chorionic gonadotropin: 24 IU per liter
  - (Normal range: <6 IU per liter)
  - Levels were 21,000 IU per liter 3 weeks earlier when pregnant
- Electrolytes, glucose, amylase, lipase, total protein, & albumin were normal
- Renal-function tests, prothrombin time, international normalized ratio and partial-thromboplastin time were normal.
- Peripheral-blood smear for babesia, a parasite that infects RBCs, were normal
- Direct antiglobulin test to determine if the cause of hemolytic anemia is due to antibodies on the RBCs were also normal
### Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults, Other Hospital</th>
<th>1 Wk before This Admission, Other Hospital</th>
<th>Reference Range, Adults, This Hospital</th>
<th>On Admission, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>37–47</td>
<td>28.2</td>
<td>36–46</td>
<td>27.5</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12–16</td>
<td>9.8</td>
<td>12–16</td>
<td>9.0</td>
</tr>
<tr>
<td>White-cell count (per mm$^3$)</td>
<td>4500–11,000</td>
<td>5900</td>
<td>4500–11,000</td>
<td>7820</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40–70</td>
<td>62</td>
<td>40–70</td>
<td>85</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>21–49</td>
<td>30</td>
<td>22–44</td>
<td>11.6</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2–10</td>
<td>6.5</td>
<td>4–11</td>
<td>3.3</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–7</td>
<td>0.2</td>
<td>0–8</td>
<td>0</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–2</td>
<td>1.3</td>
<td>0–3</td>
<td>0.1</td>
</tr>
<tr>
<td>Platelet count (per mm$^3$)</td>
<td>150,000–400,000</td>
<td>77,000</td>
<td>150,000–400,000</td>
<td>80,000</td>
</tr>
<tr>
<td>Red-cell count (per mm$^3$)</td>
<td>4,200,000–5,400,000</td>
<td>2,690,000</td>
<td>4,000,000–5,200,000</td>
<td>2,720,000</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>80–94</td>
<td>105</td>
<td>80–100</td>
<td>101</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg)</td>
<td>27–31</td>
<td>36.3</td>
<td>26–34</td>
<td>33</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (g/dl)</td>
<td>32–36</td>
<td>34.6</td>
<td>31–37</td>
<td>33</td>
</tr>
<tr>
<td>Red-cell distribution width (%)</td>
<td>10.5–14.3</td>
<td>14.2</td>
<td>11.5–14.5</td>
<td>14.6</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>0.5–2.5</td>
<td>4.5</td>
<td>0.5–2.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>9.0–11.9</td>
<td>9.2</td>
<td>11–14</td>
<td>14.9</td>
</tr>
<tr>
<td>Prothrombin-time international normalized ratio</td>
<td>0.8–1.2</td>
<td>0.9</td>
<td>0.9–1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Activated partial-thromboplastin time (sec)</td>
<td>23–32</td>
<td>28.5</td>
<td>22–35</td>
<td>28.1</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>175–425</td>
<td>417</td>
<td>150–400</td>
<td>327</td>
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<tr>
<td>D-dimer (ng/ml)</td>
<td>&lt;590</td>
<td>4400</td>
<td>&lt;500</td>
<td>9377</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)$^\dagger$</td>
<td>0.2–1.0</td>
<td>0.8</td>
<td>0–1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Haptoglobin (mg/dl)</td>
<td>43–212</td>
<td>&lt;15</td>
<td>16–199</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>100–190</td>
<td>678</td>
<td>110–210</td>
<td>487</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>31–116</td>
<td>151</td>
<td>45–115</td>
<td>165</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>7–35</td>
<td>25</td>
<td>10–55</td>
<td>29</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>10–32</td>
<td>38</td>
<td>10–40</td>
<td>25</td>
</tr>
</tbody>
</table>
Computed Tomography (CT)

- CT of the abdomen and pelvis were performed and revealed splenomegaly, abnormal enlargement of the spleen
  - Spleen length: 15.6 cm; Normal range, <12 cm
- Central filling defect in the splenic vein compatible with acute splenic-vein thrombosis
- CT of the chest showed low lung volumes, scattered opacities, and no evidence of pulmonary embolism
CT Scan of the Abdomen
Question 1

Thrombosis is described as inappropriate clotting. Which of the following is a risk factor for the development of thrombosis?

A. Inherited deficiencies of protein C or protein S
B. Smoking
C. Oral contraceptive use
D. Anti-phospholipid antibody syndrome
E. All of the above
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Discharge from Hospital

- Oral contraception was stopped
- Diminished abdominal pain by the third hospital day
- Discharged
4 Days Later

- Patient experienced severe bifrontal headache and loss of vision in the left visual field
- CT of the head and neck
- Transferred to the emergency department of Mass Gen
The patient presents with left homonymous hemianopia, or loss of vision in the left visual field. Which of the following is likely affected in this patient?

A. The left hemisphere of the brain
B. The right hemisphere of the brain
C. The optic chiasm
D. The fovea of the eye
E. The optic nerve of the left eye
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Question 2

The patient presents with left homonymous hemianopia, or loss of vision in the left visual field. Which of the following is affected in this patient?

A. The left hemisphere of the brain
B. The right hemisphere of the brain
C. The optic chiasm
D. The fovea of the eye
E. The optic nerve of the left eye
More Patient History

- Chronic back pain related to vertebral disk herniation for which she had spinal fusion surgery 4 years prior to admission
- Two episodes of self-limited thrombocytopenia thought to be associated with methotrexate treatment for an unknown skin disorder
- No family history of bleeding or clotting disorders, spontaneous miscarriage, or hematologic cancer
- 2 year history of dull epigastric pain associated with nausea and occasional episodes of bilious emesis (pain improved with omeprazole)
- Medications included: diclofenac, baclofen, controlled-release morphine sulfate, hydrocodone-acetaminophen, and omeprazole
Transferred to Massachusetts General

- Patient reported persistent headache, vision changes in the left visual field, photophobia, phonophobia, and pain with extraocular movements
- On examination
  - Temperature: 38.3°C (Normal: 36.1-37.2)
  - Blood Pressure: 126/72 mmHg
  - Respiratory Rate: 20 breaths per minute
  - Oxygen Saturation: 96%
  - Mild distress due to headache, but alert and oriented to time and place
  - Neck, heart, lungs, abdomen, skin, and oral mucosa were normal
Transferred to Massachusetts General

- Other cranial nerve functions were normal
- Strength, sensation to light touch, and deep tendon reflexes of the arms and legs were normal
- Finger-nose-finger test revealed no dysmetria
- Peripheral-blood smear showed 0-2 schistocytes per high-power field, teardrop and pencil cells, occasional large platelets, and normal white cells
- Urinalysis showed 1+ ketones, 2+ blood, 1+ protein, 1+ urobilinogen, a specific gravity greater than 1.040 (Normal range: 1.001-1.035), and pH of 5 (Normal: 5-9) by dipstick
Transferred to Mass Gen

- Microscopic examination of sediment revealed no red cells and 3-5 white cells per high-power field (Normal range: 0-2)
- Admitted to the ICU of Mass Gen
- Additional imaging studies were obtained
Images of the Head
Initial considerations:

- Recall the 32 year old had abdominal pain, vaginal bleeding, and headache 3 weeks after elective termination of pregnancy.

- Patient was confirmed to have the following:
  - **Splenic-vein thrombosis**: isolated thrombosis of splenic vein.
  - **Cerebral venous thrombosis**: presence of acute thrombosis in dural venous sinuses, drains blood from brain.
  - **Thrombocytopenia**: abnormally low levels of thrombocytes
  - **Hemolytic anemia**: red blood cells are destroyed and removed from bloodstream before their normal lifespan is over.

- Initial arguments debated on this patient’s possible for **disseminated intravascular coagulation** and **microangiopathic hemolytic anemia (MHA)**.
Disseminated Intravascular Coagulation

- Blood clots form throughout the body, which blocks small blood vessels.
- Symptoms include chest pain, shortness of breath, leg pain, problems speaking or problems moving parts of the body.
- In patient, prothrombin time was slightly prolonged, fibrinogen level was normal, and the thrombocytopenia was mild, and elevated D-dimer levels.
- With these considerations, DIC was not likely.
Table 1  Scoring system for overt Disseminated Intravascular Coagulation (DIC)

1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?
   
   * If yes: Proceed.
   *
   * If no: Do not use this algorithm.

2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, fibrin-related marker).

3. Score global coagulation test results.
   
   - Platelet count
     
     ($>100 = 0; <100 = 1; <50 = 2$)
   
   - Elevated fibrin related marker (e.g. D-dimers; fibrin degradation products)
     
     (no increase = 0; moderate increase = 2; strong increase = 3)
   
   - Prolonged prothrombin time
     
     ($<3\text{ s} = 0; >3\text{ s but }<6\text{ s }= 1; >6\text{ s }= 2$)
   
   - Fibrinogen level
     
     ($>1.0\text{ g L}^{-1} = 0; <1.0\text{ g L}^{-1} = 1$)

4. Calculate score
   
   - If $\geq 5$: compatible with overt DIC: repeat score daily
   - If $< 5$: suggestive (not affirmative) for non-overt DIC: repeat next 1–2 days.
Question 3: Which of the following could be a reason of concern for DIC?

A. Patient’s slightly prolonged prothrombin time
B. Patient’s elevated D-dimer
C. Low platelet count
D. Patient’s fibrinogen levels
E. More than one of the choices above
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Question 4: What can best explain the elevated D-dimer levels in this patient?

A. Patient’s anemia
B. Patient’s immobility
C. Patient’s thromboses
D. The patient’s age.
E. None of the above
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Microangiopathic Hemolytic Anemia

- MHA is a disorder characterized by mechanical damage of red cells - occurs with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.
- MHA can occur with malignant hypertension, eclampsia, vasculitis, and valvular heart disease.
- Examined peripheral blood smear to rule of presence of schistocytes. >1% schistocytes raises concerns of MHA
  - Fragmented part of red blood cell
- Patient had 0 - 2 schistocytes per high-power field. MHA is possible but unlikely.
Observing salient feature of the history

- No **history** of anemia, therefore it is unlikely that patient has an inherited red-cell disorder.

- Patient had 2 years of episodic abdominal pain. Acute porphyria is possible, but rare. Due to the patient’s imagings, it may be due to splenic-vein thrombosis.

- Take timing into account: the timing of her illness and elective termination of pregnancy as well as initiation of birth control.
  - High estrogen state of pregnancy as well as estrogen-containing contraceptive agent are prothrombotic.

- Events indicated above can potentially explain the thrombosis, but it doesn’t account anemia.
Question 5: Given the salient features of this patient’s history, which of the following is unlikely for the patient to have?

A. Hemoglobinopathy
B. Enzyme deficiency
C. Membrane defect
D. Sickle cell anemia
E. All of the above
Question 5: Given the salient features of this patient’s history, which of the following is unlikely for the patient to have?

A. Hemoglobinopathy  
B. Enzyme deficiency  
C. Membrane defect  
D. Sickle cell anemia  
E. All of the above
A Closer Evaluation of Laboratory Test Results

- Combination of anemia, elevated lactate dehydrogenase, and undetectable haptoglobin level → possible hemolytic anemia
  - Peripheral blood smear did not show spherocytes, seen in autoimmune hemolytic anemia, or red cell clumping
  - Coombs’ test (direct antiglobulin test) was negative, arguing against autoimmune hemolytic anemia
- Combination of anemia, thrombocytopenia, low reticulocyte count, and mean corpuscular volume → possible macrocytosis
- Urinalysis: dipstick analysis showed 2+ blood, but microscopic analysis did not show any RBCs
  - With suspected hemolytic process, this combination would suggest hemoglobinuria without hematuria
  - This pattern suggests intravascular hemolysis, rather than extravascular hemolysis
Question 6: What is the difference between intravascular hemolysis and extravascular hemolysis?

A. Intravascular hemolysis is the process of red cells removed by phagocytic monocytes; extravascular hemolysis is the process of free hemoglobin being released into the plasma

B. Intravascular hemolysis is the process of free hemoglobin being released into the plasma; extravascular hemolysis is the process of red cells removed by phagocytic monocytes

C. Intravascular hemolysis increased blood flow into tissues; extravascular hemolysis is increased blood outflow

D. Intravascular hemolysis is the breaking down of RBCs in the vasculature; extravascular hemolysis is the breaking down of RBCs in places other than the vasculature
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A Closer Evaluation of Laboratory Test Results

- Initial neurologic concerns due to escalating head pain, abdominal pain, splenic vein thrombosis, and abnormal hematologic lab test results
  - Unlikely aneurysmal subarachnoid hemorrhage and pituitary apoplexy because usually associated with sudden onset of severe thunderclap headache
  - Unlikely infectious cause because absence of fever and neck stiffness
- Sudden onset of a new focal deficit and presence of stroke risk factors made diagnosis either embolic or venous stroke in the right temporo-occipital region
Question 7: Considering the patient’s history, what are possible stroke risk factors?

A. History of smoking
B. Recent pregnancy
C. Use of oral contraceptive pills
D. B and C
E. All of the above
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A. History of smoking
B. Recent pregnancy
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D. B and C

E. All of the above
A Closer Evaluation of Laboratory Test Results

- Combination of worsening headache over a span of 1 week, recent pregnancy, initiation of oral contraception, and elevated D-dimer levels made cerebral venous thrombosis the most likely neurologic diagnosis.
- Combination of pregnancy termination with a complication of vaginal bleeding, methotrexate exposure, and oral contraceptive use could explain anemia, but not ongoing hemolysis.
- Although D-dimer level was elevated, fibrinogen level was normal and prothrombin time was only slightly prolonged, so DIC was unlikely.
- Methotrexate exposure and glucose 6-phosphate dehydrogenase deficiency could both explain hemolysis, but neither would explain thrombosis.
A Closer Evaluation of Laboratory Test Results

- Hemoglobinuria, thrombocytopenia, history abdominal pain, and unusual thrombotic events all raise concerns about Paroxysmal Nocturnal Hemoglobinuria (PNH)

- One third of female patients with PNH receive the diagnosis during pregnancy
  - Elevated estrogen levels possibly contribute to increased thrombotic risk

- Intravascular hemolysis releases free hemoglobin into the plasma, leading to scavenging of nitric oxide → smooth muscle dystonia and abdominal pain

- Macrocytosis and thrombocytopenia are prominent features of PNH
  - Poorly understood mechanisms
Clinical Diagnosis:
Cerebral venous thrombosis in context of paroxysmal nocturnal hemoglobinuria
Pathological Discussion

- PNH is an acquired, life-threatening, clonal hematopoietic stem-cell disorder caused by an acquired mutation in a gene encoding phosphatidylinositol glycan class A (PIG-A).
- Mutation inhibits expression of GPI-anchored proteins (such as CD59, CD55, CD24, and CD14) on the surface of hematopoietic cells.
- Peripheral-blood flow cytometry is a sensitive and specific way to detect decreased expression of GPI-anchored proteins.
  - Analysis uses monoclonal antibodies against specific GPI-anchored proteins (CD59, CD24, CD14) and fluorescein-labeled proaerolysin (FLAER) staining.
Question 8: What are monoclonal antibodies?

A. Antibodies that recognize several epitopes on a protein
B. Antibodies that recognize a single epitope on a protein
C. Antibodies that recognize specific amino acids of a protein
D. None of the above
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Figure 4. Results of Peripheral-Blood Flow Cytometry.

Panel A shows the level of CD59 expression in glycophrin A+ erythrocytes: approximately 1% of the glycophrin A+ erythrocytes show a partial CD59 deficiency (these are known as type II cells), and approximately 5% show a complete CD59 deficiency (type III cells). Panel B shows the level of CD24 expression and fluorescein-labeled prcaeroylsin (FLAER) staining in CD15+ neutrophils, which have a high level of side scatter of light (SSC, a marker of cytoplasmic complexity and granulation) (top graph); approximately 57% of the CD15+ neutrophils show loss of CD24 expression and no FLAER staining, a finding consistent with a paroxysmal nocturnal hemoglobinuria (PNH) clone (bottom graph). Panel C shows the level of CD14 expression and FLAER staining in CD64+ monocytes, which have a low level of SSC (top graph); approximately 60% of the CD64+ monocytes show loss of CD14 expression and no FLAER staining, a finding consistent with a PNH clone (bottom graph).
Discussion of Management

- Patient has hemolysis, thrombosis & PNH with absence of bone marrow dysfunction → classic PNH
  - Rare disorder with unusual clinical features
- 40% of patients have thrombosis which can be life-threatening
- Treated with unfractionated heparin and transitioned to warfarin
- Treated with folic acid, iron supplement, medroxyprogesterone
Unfractionated heparin is used as a therapeutic anti-coagulant but 5% of patients can develop Heparin-induced thrombocytopenia (HIT) syndrome. HIT is characterized by

A. Development of autoantibodies that bind to heparin
B. Development of autoantibodies to platelet derived growth factor
C. Development of autoantibodies to platelet membrane protein
D. Both A and B
E. Both A and C
Question 9

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Options to Treat PNH

- Eculizumab -- humanized monoclonal antibody which blocks conversion of C5 and formation of C5-9 (membrane attack complex)
- Protects PNH-associated RBC from complementary intravascular hemolysis
- Eculizumab is safe, reduces hemolysis, fatigue, risk for thrombosis and need for bone marrow transfusion → better quality of life!
- Before Eculizumab survival was 10 years
- Now -- 6-year overall survival rate is 92%
Options to Treat PNH

- Bone marrow transplant -- curative treatment
- Clinically significant morbidity and mortality -- 5 year survival is 68%
- Today, bone marrow transplant is only used for PNH with:
  - Concurrent severe aplastic anemia
  - Myelodysplastic syndrome
  - No response to Eculizumab OR unable to afford the high cost of drug
Question 10

Bone marrow transplant, also known as hematopoietic stem cell transplant, used to be a common treatment for PNH. However it has a lower success rate compared to pharmaceutical therapy. Why could this transplant be rejected?

A. Anti-thymocyte globulin
B. Cyclosporine
C. Graft-Versus-Host Disease (GVHD)
D. All of the above
E. None of the above
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C. **Graft-Versus-Host Disease (GVHD)**
D. All of the above
E. None of the above
Management of PNH

- Patient was administered Eculizumab and monitored for hemolysis weekly for 4 weeks and then monthly
- Developed common side effects: headaches, nasopharyngitis, nausea, back pain, dizziness and fatigue
- Side effects dissipated by week 26 of therapy → normal timeline
- Still had mild anemia and a positive Coombs test
  - Patient still has extravascular hemolysis
  - Eculizumab only treats intravascular hemolysis
Management of PNH

- Several months later -- patient has persistent thrombocytopenia and anemia
- Bone marrow biopsy to test for aplastic anemia and myelodysplastic syndrome
  - Both cause anemia in PNH
- No evidence of either disorder
- 1 year later patient is doing well!
Lesson Learned from Case

From the Patient:

● With new complex diagnoses, doctors should take the time and patience to explain the condition to the patient
● Give the patient time to process, research and ask questions
● Time doctors took explain diagnosis and what to expect made a HUGE difference for the patient
● Being there helped to humanize a rare and complex diagnosis