Pernicious Emboli: An Uncommon Cause of a Common Problem

Daniel Ambinder, MD; Alison Moliterno, MD; Michael Streiff, MD; Bennett Clark, MD

Department of Medicine, Johns Hopkins University School of Medicine
Debbi Ravert, MD
UMSOM, Class of 2014
Resident, JHH EM

Have I have a great case for you....
Case Presentation

• 51 year old woman with HTN presents with **sudden-onset shortness of breath**

• Associated with: **diaphoresis**, **lightheadedness** and **near-syncope**

• Occurred while walking outdoors but persisted despite resting on a park bench

• Family members reported recent development of fatigue, drowsiness and forgetfulness
Case Presentation

• **Pertinent negatives:**
  
  Chest pain, orthopnea, PND, palpitations, cough, wheezing, sputum production, melena, hematochezia, vomiting, fevers or chills

• **Review of systems:**
  
  Six month gradual development of paresthesia, impaired memory, fatigue and gait instability.
History

- **PMH/PSH:**
  - Hypertension
  - Hyperlipidemia
  - No prior history of heart, lung, or GI disease

- **Social History:**
  - Former smoker – quit a few months ago
  - Denies alcohol, denies illicit drug use

- **FH:** No early MI, no clotting disorders, no thyroid problems

- **Medications:** Lisinopril 10mg daily, not taking reliably

- **Allergies:** None
ED VS: T 36.5 | P 112 | BP 130/80 | RR 16 | SpO2 94% on RA

- **General:** Diaphoretic but in no acute distress.
- **CV/PULM:** No RV heave or JVD, lungs clear
- **Extremities:** Shallow pitting edema extending to the knees bilaterally
- **Neuro:**
  - Gait was slightly wide based and showed a tendency for retropulsion
  - Inability to recall three objects, increased irritability
  - Sensation and deep tendon reflexes preserved
Initial imaging:

Chest X-Ray: Unremarkable
CT Head/Brain WO Contrast

IMPRESSION:
No CT evidence of an acute intracranial abnormality
Impression:
No evidence of deep vein thrombosis in the bilateral lower extremities veins as described.
Initial labs

**CBC**
- Hb: 7.7 g/dL
- HCT: 23.1%
  - MCV 106.9 fL
- WBC: 7.3K
- Plts: 170K

**BMP**
- Na: 142
- K: 3.6
- Cl: 105
- CO2: 22
- AG: 15
- Glucose: 89
- BUN: 11
- Cr: 1.0
- Ca: 8.5
- Mg: 1.8

**Liver Panel**
- AST: 22
- ALT: 16
- Alk Phos: 75
- T Bili: 2.8 / DB: 0.5
- T Protein: 7.1
- Albumin: 4.1

**Troponin I**: 0.06 -> 0.2 (9H)
LDH: 650
TSH: 1.20
FOBT: negative

**Coags**
- PT: 14.3
- INR: 1.4
- aPTT: 23.7
Hemolytic or Hypoproliferative?

- Hb: 7.7 g/dL  |  HCT 23.1
- MCV 106.9 fL
- T Bili: 2.8
- LDH: 650
- PT 14.3 | INR 1.4 | aPTT 23.7
- Troponin I: 0.06 -> 0.2 (9H)
Reticulocytes - the first clue

- Absolute retic count: 12.9 (24.1-87.7 K)
The Predictive Value of Serum Haptoglobin in Hemolytic Disease

Anthony Marchand, MD; Robert S. Galen, MD, MPH; Frederick Van Lente, PhD

<table>
<thead>
<tr>
<th>LDH</th>
<th>Haptoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Haptoglobin – the second clue

Haptoglobin↑↓

90% specific for hemolysis

nl

Rules out hemolysis (92%)

>25

Hemolysis is unlikely

Case 650 (H)

68 (36 - 195)

Hemolysis is unlikely
Sudden onset Dyspnea

Tachycardia

Bilateral pedal edema X 2 weeks (new)
IMPRESSION:

1. Extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

2. No CT evidence of right heart strain.
Paresthesia
Impaired memory
Gait instability
Macrocytosis

<table>
<thead>
<tr>
<th>Measured</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12, Serum</td>
<td>33 pg/mL</td>
</tr>
<tr>
<td></td>
<td>211-946</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>200 umol/L</td>
</tr>
<tr>
<td></td>
<td>4.0-15.2</td>
</tr>
<tr>
<td>MMA</td>
<td>8770 nmol/L</td>
</tr>
<tr>
<td></td>
<td>45-325</td>
</tr>
<tr>
<td>Intrinsic Factor Ab</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>
Methylcobalamin

Vitamin B₁₂ (Cobalamin)

Methylmalonyl-CoA

Methionine (Methylation)

Homocysteine

5-Methyltetrahydrofolate

Tetrahydrofolate (DNA synthesis)

Succinyl-CoA

Methylmalonyl-CoA mutase

Adenosylcobalamin

Methyltransferase
Peripheral Blood Smear

- Hypersegmented neutrophils
- Macrocytosis, poikilocytosis, fragments, bites, ovalocytes and teadrops.
MRI of Brain: T2 FLAIR

IMPRESSION:

- High signal intensity in the cerebellar hemispheres bilaterally
  - described in the Journal of child neurology 2013 December in vitamin B12 deficiency.
Congenital Homocystinuria

- Mutation in the cystathionine beta-synthase gene
- Autosomal recessive
- Ectopic lentis, myopia and other abnormalities
- Thromboembolism is the most common cause of death
Last 11 cases see at JHH with B12 deficiency

- 4/11 had VTE
- 3/11 referred for TMA and plasma exchange

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Presentation / Diagnosis</th>
<th>B12</th>
<th>HCY 4-12</th>
<th>MMA 90-279</th>
<th>VTE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>F</td>
<td>pancytopenia, neuropathy, AMS, TMA</td>
<td>30</td>
<td>108.6</td>
<td>83050</td>
<td>-</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>PE</td>
<td>62</td>
<td>144</td>
<td>4160</td>
<td>Y</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>PE, anemia, neurological sxss</td>
<td>33</td>
<td>200</td>
<td>8770</td>
<td>Y</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>anemia, fatigue, paresthesias</td>
<td>48</td>
<td>49.5</td>
<td>21400</td>
<td>-</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>dizzy, anemia, “TMA”</td>
<td>30</td>
<td>123.3</td>
<td>39490</td>
<td>-</td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>fatigue, jaundice</td>
<td>45</td>
<td>105</td>
<td>5056</td>
<td>-</td>
</tr>
<tr>
<td>73</td>
<td>M</td>
<td>glossitis, fatigue, dyspepsia, FTT</td>
<td>33</td>
<td>189.4</td>
<td>175000</td>
<td>-</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>syncope, fatigue</td>
<td>42</td>
<td>-</td>
<td>2320</td>
<td>-</td>
</tr>
<tr>
<td>67</td>
<td>F</td>
<td>DVT, fatigue</td>
<td>62</td>
<td>-</td>
<td>-</td>
<td>Y</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>pancytopenia, “TMA”</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>44</td>
<td>M</td>
<td>PE (syncope, dyspnea)</td>
<td>95</td>
<td>92.4</td>
<td>431</td>
<td>Y</td>
</tr>
</tbody>
</table>
Management

• IV heparin infusion initiated and bridged with enoxaparin to warfarin with an overlapping regimen of enoxaparin.

• Pernicious anemia was managed with intramuscular vitamin B12 repletion followed by oral B12 indefinitely.
Follow Up

• The patient returned to clinic 7 months later, having continued vitamin B12 supplementation.

• Anticoagulation was discontinued

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>12.8</td>
<td>7.7 (L)</td>
<td>13.0</td>
</tr>
<tr>
<td>12.0-15.0 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39.9</td>
<td>23.1 (L)</td>
<td>41.3</td>
</tr>
<tr>
<td>36.0-46.0 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>82.8</td>
<td>106.9 (H)</td>
<td>83.9</td>
</tr>
<tr>
<td>80.0-100.0 fl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Corpus Hgb</td>
<td>26.6</td>
<td>35.6 (H)</td>
<td>26.4</td>
</tr>
<tr>
<td>26.0-34.0 pg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC Distribution Width</td>
<td>13.6</td>
<td>16.7 (H)</td>
<td>14.0</td>
</tr>
<tr>
<td>11.5-14.5 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin,Total</td>
<td>0.4</td>
<td>2.8 (H)</td>
<td>0.5</td>
</tr>
<tr>
<td>0.0-1.2 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Dimer</td>
<td>20.84 (H)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>0.17-0.88 mg/L FEU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>33 (L)</td>
<td>922</td>
<td></td>
</tr>
<tr>
<td>211-946 pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylmalonic Acid, Serum</td>
<td>8770 (H)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td>200.0 (H)</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>4.0-15.2 umol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
… But the best part of it is

- Full neurologic recovery
- Moved out of her daughter’s home and lives independently
- Began driving for the MTA
Take home points

- B12 deficiency can present similarly to a micropathic hemolytic anemia

- Decreased reticulocyte count, elevated LDH and normal Haptoglobin can help distinguish the two states

- B12 deficiency is a potentially reversible cause of thrombophilia
Acknowledgements

- Debra Ravert, MD
- Michael Streiff, MD
- Alison Moliterno, MD
- Bennett Clark, MD
References:

Vitamin B12 deficiency is a well described condition that leads to macrocytic anemia and neuropsychiatric disorders.

B12 absorption requires several steps that include stomach acid facilitating breakdown of the vitamin bound to food, secretion of intrinsic factor (IF) by gastric parietal cells, the binding of IF and B12 in the duodenum, and the complex is absorbed in terminal ileum.

Pernicious anemia is an autoimmune process where an autoantibody to intrinsic factor is produced leading to atrophic gastritis and B12 deficiency.

B12 acts as a cofactor in the conversion of methylmalonic acid (MMA) to succinyl-coenzyme A and homocysteine to methionine.

In the absence of B12, levels of neurotoxic MMA increase driving peripheral neuropathies, subacute combined degeneration of the spinal cord, dementia and memory loss. Inability to convert homocysteine to methionine leads to macrocytic anemia and in severe cases, pancytopenia.

DIAGNOSIS

- Dyspnea, tachycardia, and EKG findings prompted a spiral CT of the chest which revealed extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs
- Constellation of paresthesia, impaired memory, gait instability, and macrocytosis raised concern for a hypoproiferative anemia caused by vitamin B12
- Serum levels of B12, homocysteine, and methylmalonic acid levels are shown below

ENHANCED FIBRIN D VIABILITY ASSAY

- ED Vitals: T 36.5, P 112, BP 130/80, RR 16, SpO2 94%
- Shallow pitting edema extended to the knees bilaterally.
- Gait was slightly wide based and showed a tendency for retropulsion
- Mental status examination was notable for an inability to recall three objects at an interval of three minutes.

Sensations to light touch and deep tendon reflexes were preserved.

A peripheral smear demonstrating macrocytic anemia with poikilocytosis, fragments, bites, ovalocytosis and tear drops consistent with macrocytic anemia.

B: Hypersegmented neutrophils

C: CT PE protocol demonstrating extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

ED Vitals: T 36.5, P 112, BP 130/80, RR 16, SpO2 94%

Dyspnea, tachycardia, and EKG findings prompted a spiral CT of the chest which revealed extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

Mental status examination was notable for an inability to recall three objects at an interval of three minutes.

Sensation to light touch and deep tendon reflexes were preserved.

A peripheral smear demonstrating macrocytic anemia with poikilocytosis, fragments, bites, ovalocytosis and tear drops consistent with macrocytic anemia.

B: Hypersegmented neutrophils

C: CT PE protocol demonstrating extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

REFERENCES

2. Thrombosis et al. Deep vein thrombosis is associated with acute intravascular hemolysis in glucose-6-phosphate dehydrogenase deficiency in a case with internal derangement.
3. Oger et al. Intrinsic factor antibodies confirm the diagnosis of pernicious anemia.
4. INHIBITIONS TO FIBRIN D VIABILITY ASSAY

- 33 pg/mL (nl 211-946)
- 200 umol/L (nl 4.0-5.2)
- 6770 nmol/L (nl 45-325)

DIAGNOSIS

- Dyspnea, tachycardia, and EKG findings prompted a spiral CT of the chest which revealed extensive pulmonary emboli within segmental branches of pulmonary arteries of both lungs
- Constellation of paresthesia, impaired memory, gait instability, and macrocytosis raised concern for a hypoproiferative anemia caused by vitamin B12
- Serum levels of B12, homocysteine, and methylmalonic acid levels are shown below

ENHANCED FIBRIN D VIABILITY ASSAY

- ED Vitals: T 36.5, P 112, BP 130/80, RR 16, SpO2 94%
- Shallow pitting edema extended to the knees bilaterally.
- Gait was slightly wide based and showed a tendency for retropulsion
- Mental status examination was notable for an inability to recall three objects at an interval of three minutes.

Sensations to light touch and deep tendon reflexes were preserved.

A peripheral smear demonstrating macrocytic anemia with poikilocytosis, fragments, bites, ovalocytosis and tear drops consistent with macrocytic anemia.

B: Hypersegmented neutrophils

C: CT PE protocol demonstrating extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

ED Vitals: T 36.5, P 112, BP 130/80, RR 16, SpO2 94%

Dyspnea, tachycardia, and EKG findings prompted a spiral CT of the chest which revealed extensive pulmonary emboli within segmental branches of pulmonary arteries of both lungs.

Mental status examination was notable for an inability to recall three objects at an interval of three minutes.

Sensation to light touch and deep tendon reflexes were preserved.

A peripheral smear demonstrating macrocytic anemia with poikilocytosis, fragments, bites, ovalocytosis and tear drops consistent with macrocytic anemia.

B: Hypersegmented neutrophils

C: CT PE protocol demonstrating extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

REFERENCES

2. Thrombosis et al. Deep vein thrombosis is associated with acute intravascular hemolysis in glucose-6-phosphate dehydrogenase deficiency in a case with internal derangement.
3. Oger et al. Intrinsic factor antibodies confirm the diagnosis of pernicious anemia.
4. INHIBITIONS TO FIBRIN D VIABILITY ASSAY

- 33 pg/mL (nl 211-946)
- 200 umol/L (nl 4.0-5.2)
- 6770 nmol/L (nl 45-325)