Profound anemia and thrombocytopenia in a former candy man

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Clinical Vignette - October 1, 2016
Presentation

• 71 year old male, with shortness of breath and fatigue
  – Progressive over 2 months
  – No associated sputum production or cough
  – Denies chest pain, abdominal pain, stool changes
  – No recent medication changes; missed insulin PM

ROS

+ Recent unsteady gait, near falls
+ More withdrawn and depressed, family very concerned
+ 15 pound weight loss over 3 months
Past Medical History

• Type 1 DM – 32 years insulin dependent
• HTN
• CKD III (baseline SCr 1.3)

Past Surgical History

• Cholecystectomy

Past Family History

• Father – coronary disease, MI, died in 80s
Home Medications

- insulin glargine 26 units nightly
- insulin lispro 10 units with meals
- telmisartan-HCTZ 80-12.5mg 1 tab BID
- aspirin 81mg daily
- acetaminophen 500mg q6 PRN
Social History

- Active cigarette smoker (½ ppd), 50 pack years
- Drinks 1-2 cocktails nightly
- Has lived in Maine entire life
- Widower for 4 years, lives in in-law apartment near grandson
- Retired, previously worked in the candy sales industry
CURTIS & SON,
PORTLAND, MAINE, U. S. A.
The First Manufacturers of
CHEWING GUMS
ESTABLISHED 1850.

SPRUCE—State of Maine, American Flag, Trunk.
PARAFFINE—White Mountain, Sugar Cream,
         New Clipse and Mastic.
CHICLE—Zapote, Taffy Tolu, Oriental Tolu, Ko
        Ko, Portland, 100 and 200 Lumps.

The Yankee Spruce Gum is
refined with great care, from
the best selected gums and
fully retains all the spicy, nat-
ural flavor. It is never crumbl
y or pitchy. Nature's own rem-
edy for heartburn and acidity
of the stomach.

CURTIS & SON, Portland, Me.
Physical Exam

- VITALS: 96/53, HR = 94, T = 36.4°C, RR = 26
- GEN: Elderly male, tan appearing, appears calm, deep breathing, flat affect
- HEENT: No oral lesions, scleral icterus+, good dentition, normal appearing tongue
- NECK: no palpable adenopathy
- CV: normal rate, reg rhythm, no murmurs, no gallop
- PULM: Clear to auscultation
- ABDOMEN: non-obese, non-tender, no HSM
- EXT: normal appearing, no bruising or lesions
- NEURO: CN 2-12 in tact, peripheral sensation normal, reflexes 2+ and symmetric.
MCV: 131.9 fL
MCHC: 36
RDW SD: 69.1 fL (37-48)
AST: 19
ALT: 10
Alk Phos: 122
Albumin: 3.8
T Bili: 3.5
Direct: 0.8
Anion Gap: 21
Ketones: +
Lactate: 0.8
Haptoglobin: <20
Lactate Dehydrogenase: 1573 U/L
Additional Lab Work-up

- Coomb’s Test: **Negative**

- Reticulocyte Count
  - Absolute: 14
  - Percent: 1.3%
  - Index: 0.3%

(>3% = normal / appropriate marrow response to anemia)
Quick re-cap

- Previously well 71 year old male with SOB, progressive fatigue
- Hypoproliferative, macrocytic anemia with evidence of hemolysis
- Type 1 DM, in DKA
- Worsening depression, ?gait instability
Peripheral Blood Smear
Bone Marrow Biopsy
MEGALOBLASTIC ANEMIA
Megaloblastic Anemia

- Folate deficiency
- Vitamin B12 deficiency
- Myelodysplastic Syndrome
- Acute Erythroleukemia
- Congenital Dyserythroidemic anemia
- Reverse Transcriptase inhibitors

$>20\text{ng/mL}$

1. No dysplasia
2. Cytogenetics testing normal
Serum Vitamin B12: <150 pg/mL

Intrinsic Factor antibody
Vitamin B12 deficiency

- Anemia
- Thrombocytopenia
- Hemolysis
Questions / thoughts?

View of Borestone Mountain from Sebec Lake
Learning Objectives

• Review sources, handling of B12
• Discuss prevalence B12 deficiency
• Discuss common manifestations
• Identify those at risk for B12 deficiency
• Consider severe hematologic manifestations of B12 deficiency
Vitamin B12 = Cobalamin

• Not synthesized by humans

• Processing
  – Cobalamin released from food by gastric acid
  – Joins intrinsic factor (parietal cells)
  – Absorption in terminal ileum

• Hepatic storage
Prevalence

Age (years)

Percent B12 deficient

20-39: 3
40-59: 4
>70: 6
Who is at risk?

• Decreased gastric acid / high pH
• Low intrinsic factor
• Malabsorption
• Low Intake
• Genetic Factors
Decreased Gastric Acid

• Atrophic gastritis
• Medications
  • PPI, H2 blockers

Low Intrinsic Factor

• Pernicious anemia
• H. pylori infection
• Post-gastrectomy syndrome

Malabsorption

• Crohn’s Disease
• Celiac Disease
• Metformin
• Small Intestinal Bacterial Overgrowth
• *Diphyllobothrium latum* (fish tapeworm)
Inadequate Intake
• Pure Vegans
• Vegetarians
• Elderly
• Alcoholics

Genetic Factors
• Transcobalamin deficiency
• Imerslund-Grasback Syndrome
Manifestations of Cobalamin Deficiency

• Hematologic
  – Anemia, Leukopenia, Thrombocytopenia

• Gastrointestinal
  – Glossitis
  – Gastritis, nausea, constipation

• Neurologic
  – Memory impairment
  – Paresthesia, loss vibratory sense, ataxia
  – Mood changes, depression, psychosis
Hematopoiesis and Vitamin B12

- Critically important
- Pancytopenia
  - Vitamin B12 key in DNA synthesis
  - Ineffective erythropoiesis = lysis within marrow cavity
Wait, could this be TTP?
Megaloblastic Anemia from Severe Vitamin B12 Deficiency

≡

Pseudothrombotic Microangiopathy

≡

Pseudo-TTP
Pseudothrombotic Microangiopathy

• Pernicious anemia

• Compared to TTP?
  – Low reticulocyte index
  – Absence of fever, neurologic symptoms, renal involvement
  – ADAMST13 levels NORMAL
  – Plasma exchange therapy not helpful

• Early consultation with hematology
Patient Course

Hematologic

• Started on intramuscular cobalamin x7 days, continuing intramuscular 1x per week for 2 month

• Well tolerated, energy levels increase
Reticulocyte Response

Day 2 = IM Vitamin B12

- Percent Reticulocytes
- Reticulocyte Index

Day 0

Day 7

Day 0:
- Percent Reticulocytes: 0.3
- Reticulocyte Index: 1.3

Day 7:
- Percent Reticulocytes: 15.5
- Reticulocyte Index: 4.2
Hemoglobin and Hematocrit

<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin (g/dL)</th>
<th>Hematocrit (%)</th>
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<tbody>
<tr>
<td>28-Jul</td>
<td>17.5</td>
<td>6</td>
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<tr>
<td>29-Jul</td>
<td>20.9</td>
<td>6.6</td>
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<tr>
<td>30-Jul</td>
<td>19.5</td>
<td>7.5</td>
</tr>
<tr>
<td>31-Jul</td>
<td>22.7</td>
<td>7.7</td>
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<tr>
<td>1-Aug</td>
<td>21.8</td>
<td>7.2</td>
</tr>
<tr>
<td>2-Aug</td>
<td></td>
<td>7.9</td>
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<tr>
<td>3-Aug</td>
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<td>4-Aug</td>
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<td>10-Aug</td>
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<tr>
<td>11-Aug</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Graph showing the increase in Hemoglobin (g/dL) and Hematocrit (%) from 28-Jul to 11-Aug.
Neuropsychiatric

• Patient began feeling much better throughout hospitalization

• As of 9/20:
  – Has re-engaged with his family, “outgoing”
  – “He is his normal self again.”

• Improvement secondary to…….?  
  – Resolution of anemia
  – Psychiatric symptoms from low B12
Summary

• Consider vitamin B12 deficiency as a cause of “hemolytic anemia” (pseudothrombotic microangiopathy)

• Assess reticulocytosis, evidence of neurologic symptoms, fever, and renal involvement to differentiate from TTP
  — Early involvement of hematologist

• Vitamin B12 deficiency common amongst elderly, other specific patient populations
Special thanks to:

- Dr. Steve Hayes (MMC, Westbrook IM)
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- Dr. Matt Dugan (NECS)
- Dr. Rob Christman (Spectrum Pathology)
- Warene Eldridge (Maine ACP)
- ACP Mentors, MMC Faculty
References

- Rannelli L. Vitamin B12 deficiency with combined hematological and neuropsychiatric derangements: a case report. Med Case Report 2014; 8; 277-280.
- Zittan E. High frequency of vitamin B12 deficiency in asymptomatic individuals homozygous to MTHFR C677T mutation is associated with endothelial dysfunction and homocysteinemia. Am J Heart Physio 2007; 293; H860-H865.
Thank you! Questions?
• Wide variation in reference range, laboratory assay
Table 1. Causes and Treatment of Vitamin B₁₂ Deficiency.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malabsorption</td>
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<tr>
<td>Pernicious anemia (autoimmune gastritis)</td>
<td>Intramuscular cyanocobalamin at a dose of 1000 μg administered intramuscularly daily or every other day for 1 wk, then weekly for 4 to 8 wk, and then monthly for life, or oral cyanocobalamin at a daily dose of 1000 to 2000 μg for life†</td>
<td>Administer iron and folate replacement as needed for full hemoglobin response, especially in patients with intestinal disease; perform surveillance for other autoimmune conditions, especially thyroid disease in patients with pernicious anemia; perform upper endoscopy in patients with symptoms of gastric cancer‡ or iron deficiency</td>
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<tr>
<td>Total or partial gastrectomy</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
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<tr>
<td>Gastric bypass or other bariatric surgery</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
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<tr>
<td>Ileal resection or organ reconstructive surgery (ileal conduit diversion and ileocecostomyplasty)</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
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<tr>
<td>Inflammatory bowel disease, tropical sprue</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
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<tr>
<td>Imerslund–Gräsbeck and other syndromes‡</td>
<td>Same as for pernicious anemia</td>
<td>Genetic counseling to detect vitamin B₁₂ deficiency in family members</td>
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<tr>
<td>Mild malabsorption</td>
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<tr>
<td>Protein-bound vitamin B₁₂ malabsorption</td>
<td>Oral cyanocobalamin at a dose of 500 to 1000 μg daily or intramuscular cyanocobalamin at a dose of 1000 μg daily or every other day for 1 wk, then weekly for 4 to 8 wk, and then monthly for life</td>
<td>Perform tests for iron deficiency, anemia of chronic kidney disease, and anemia of chronic inflammation; these conditions coexist frequently in older adults, may limit the response to treatment, and may require further treatment</td>
</tr>
<tr>
<td>Mild atrophic gastritis</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
</tr>
<tr>
<td>Use of metformin¹⁴</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
</tr>
<tr>
<td>Use of drugs that block stomach acid</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
<td>Same as for protein-bound vitamin B₁₂ malabsorption</td>
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<tr>
<td>Dietary deficiency</td>
<td></td>
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<tr>
<td>Adults</td>
<td>Supplements containing &gt;2 μg of vitamin B₁₂ or foods fortified with vitamin B₁₂</td>
<td>Perform tests for iron deficiency, which is very common</td>
</tr>
<tr>
<td>Infants</td>
<td>Intramuscular cyanocobalamin at a dose of 250 to 1000 μg daily, then weekly until patient recovers; treatment of mother to enrich breast milk; oral supplementation with 1 to 2 μg of vitamin B₁₂ daily or vitamin B₁₂–enriched formula or food</td>
<td>Confirm metabolic response in infants or refer parents to genetics specialist for evaluation; provide nutritional counseling for mothers</td>
</tr>
<tr>
<td>Children</td>
<td>100 μg of intramuscular vitamin B₁₂ monthly or high-dose oral vitamin B₁₂ daily in younger children; treatment as per adults in older children</td>
<td>Confirm pernicious anemia or congenital malabsorption</td>
</tr>
<tr>
<td>Recreational or occupational abuse of nitrous oxide§</td>
<td>Intramuscular cyanocobalamin on the same schedule as that for pernicious anemia above and for life if underlying pernicious anemia is present</td>
<td>Evaluate for vitamin B₁₂ malabsorption; provide addiction counseling</td>
</tr>
<tr>
<td>Nitrous oxide anesthesia in occult pernicious anemia²⁷</td>
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</tbody>
</table>

* Intramuscular hydroxocobalamin can be substituted for intramuscular cyanocobalamin, but document the long-term response if it is administered at 3-month intervals.
† Experts are not in agreement about the necessity or frequency of routine upper endoscopy in patients with pernicious anemia. However, symptoms suggestive of gastric carcinoma, unexplained iron deficiency, and proven gastrointestinal blood loss should prompt a full investigation.
‡ Congenital malabsorption of vitamin B₁₂ results from mutations of the ileal cubam receptor, cubilin, or amnionless (as in the Imerslund–Gräsbeck syndrome) and from mutations in gastric intrinsic factor. These syndromes are usually manifested in infancy and early childhood, although studies have shown a delay in onset even into adolescence.
§ Nitrous oxide inactivates the vitamin B₁₂–dependent enzyme methionine synthase and causes formation of vitamin B₁₂ analogues and gradual tissue depletion of vitamin B₁₂.
Labs

- Vitamin B12 level: <150pg/mL (211-946pg/mL)
- Methylmalonic acid: 2.41nmol/mL (<0.4nmol/mlL)
- Homocysteine: 36.5umol/L (<13.9umol/L)
- Intrinsic Factor Antibody: Positive
Vitamin B12 and Cardiovascular Effects

- Anemia

- Elevated homocysteine

- Numerous cohort studies
  - Longitudinal, 30 years and counting
  - No association with increased CV events
• Troponin: 0.15 → 2.9
  – Remained chest pain free

• Echocardiogram
  – Severely reduced left ventricular ejection fraction estimated @ 27%
  – Mid apical and septal hypokinesis

• CXR
  – Small bilateral effusions, hilar prominence
Cardiovascular

• Regadenosine Nuclear Stress Test (6 days later)
  – Fixed area of ischemia consistent with prior infarct
  – EF estimated @ 50%

• Started on medical therapy for cardiomyopathy

• Type II NSTEMI (supply/demand mismatch)