THE NECKER SYNDROME

Sarah Buckley
Dan Martin
January 2015
TTP AND MDS

(OR SOMETHING IN BETWEEN)
CC: 74 yo F presenting with anemia, thrombocytopenia, renal insufficiency, and altered mental status.

HxPI: - Last seen “normal” 2 weeks prior
- **Found down** 1 day prior at home surrounded by blood and feces

PMHx: - Unprovoked DVT/PE 4 months prior
- Several months of emesis after eating

MEDS: - Warfarin

FamHx: - No cancer, autoimmune disease, thrombosis
CC: 74 yo F presenting with anemia, thrombocytopenia, and altered mental status.

EXAM:
- VSS, well appearing after volume resuscitation
- HEENT: no icterus, no oral lesions
- NEURO: A/O x3, declined rest of exam

<table>
<thead>
<tr>
<th>WBC</th>
<th>RBC</th>
<th>Hgb</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>117</td>
<td>57</td>
<td>169</td>
</tr>
<tr>
<td>4.6</td>
<td>20</td>
<td>3.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Diff: 83% PMN, 17% LYM, 2% NRBC

- Tbili: 2.9
- LDH: 3981
- RI: 1.2%
- Hapto: <10
- UA: 1+ BLD, 0 RBC
- ADAMTS13: pending
CC: 74 yo F presenting with anemia, thrombocytopenia, and altered mental status.

INITIAL MANAGEMENT
- Therapeutic plasma exchange x3 days
- No improvement in Hct or Plts

A DIAGNOSTIC TEST WAS PERFORMED…
CC: 26 yo M presenting with syncope and pancytopenia.

HxPI: - 1 month of fatigue, vomiting, diarrhea, headaches
- Syncopized, “out” for 30 seconds

PMHx: None
MEDS: None

SocHx: - Unemployed, smokes tobacco and MJ.
FamHx: - Vitiligo
CC: 26 yo M presenting with syncope.

EXAM:
- VSS, well appearing
- NEURO: A/O x3, normal strength / sensation
CC: 26 yo M presenting with syncope.

EXAM:
- VSS, well appearing
- HEENT: no icterus, no oral lesions, glossitis
- NEURO: A/O x3, normal strength / sensation
- SKIN: hypopigmented patches

<table>
<thead>
<tr>
<th>Tbili</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>5050</td>
</tr>
<tr>
<td>ARC:</td>
<td>40</td>
</tr>
<tr>
<td>Hapto</td>
<td>&lt;10</td>
</tr>
<tr>
<td>UA</td>
<td>2+ BLD, 0 RBC</td>
</tr>
</tbody>
</table>

ANC 600
NRBCs 4%
Diff 2% UNCLASS
Morph "unclassified cells are blasts"

MCV 92
Peripheral blood
Peripheral blood
Flow: myeloblasts are slightly increased in number (6.7%) and have slightly increased CD4 and CD123. These changes are not sufficient for the diagnosis of a myeloid stem cell disorder.
A DIAGNOSTIC TEST WAS PERFORMED…

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Anti-intrinsic factor Ab</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-parietal cell Ab</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>B12 repletion</td>
<td>1000 mcg IM daily x4</td>
<td>1000 mcg IM daily x3</td>
</tr>
<tr>
<td></td>
<td>1000 mcg IM monthly</td>
<td>1000 mcg IM weekly x4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 mcg IM monthly</td>
</tr>
<tr>
<td>Outcome</td>
<td>All hematologic abnormalities resolved</td>
<td></td>
</tr>
</tbody>
</table>
Two cases

Background

“Pseudo-TTP”

B12 and cancer

Treatment
ROLE OF B12 CELL FUNCTION

1. Methyl-THF $\rightarrow$ THF $\rightarrow$ DNA Synthesis

$\downarrow$ B12 $\downarrow$

Methyl-B12

Methionin $\rightarrow$ Homocystein $\uparrow$

2. Myelin destabilization $\leftarrow$ MMA $\uparrow$

Succinyl CoA

Methylmalonyl-CoA mutase $\downarrow$

B12 $\downarrow$
CAUSES OF B12 DEFICIENCY

**DIET**
- Vegans
- Vegetarian diet in pregnancy

**GASTRIC**
- Pernicious anemia
- Gastric bypass

**SMALL BOWEL**
- Ileal resection
- Malabsorption
- Transcobalamin II deficiency
- Fish tapeworm

**EXOGENOUS BLOCKERS**
- Neomycin
- Metformin
- PPI / H2 blockers

The New Yorker, 1/22/01

UpToDate, Causes of vitamin B12 deficiency.
PRESENTATION OF VITAMIN B12 DEFICIENCY

Signs and Symptoms

1. **Neuropsychiatric**: paresthesias, loss of position / vibration sense, weakness, irritability, impaired memory, paranoia
2. **Gastrointestinal**: glossitis, nausea, vomiting, diarrhea
3. **Metabolic**: osteopenia

Laboratory Findings

1. **Cytopenias**: ineffective production, destruction of erythrocyte precursors, hypersegmented neutrophils
2. **Auto-antibodies**: anti-intrinsic factor, anti-parietal cell

Two cases

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TTP vs. PSEUDO-TTP

MCV
Creatinine
B12

LDH
Retics
MMA/HCY

FIG. 1  Plasma LDH levels in patients with markedly megaloblastic bone marrow (14.6 g. = 100).
Rough JK, Severe vitamin B12 deficiency mimicking TTP. Blood 2014
Bain BJ. Schistocytoses in megaloblastic anemia. AJH 2010.
OUTLINE

Two cases

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TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY
FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

Sidney Farber, M.D.,† Louis K. Diamond, M.D.,‡ Robert D. Mercer, M.D.,§
Robert F. Sylvester, Jr., M.D.,¶ and James A. Wolff, M.D.||

BOSTON

The Action of Pteroylglutamic Conjugates on Man.
Farber S, Cutler EC, Hawkins JW, Harrison JH, Peirce EC 2nd, Lenz GG.
PERNICIOUS ANEMIA & CANCER RISK

Retrospective study of VA patients with new diagnosis of PA

5000 men identified

<table>
<thead>
<tr>
<th>Cancer</th>
<th>1 yr SIR</th>
<th>7 yr SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid leukemia</td>
<td>13.51</td>
<td>3.66</td>
</tr>
<tr>
<td>Gastric</td>
<td>7.55</td>
<td>3.21</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.14</td>
<td>2.10</td>
</tr>
</tbody>
</table>

CHROMOSOMAL INSTABILITY

Cytogenetic observations from 14 patients with B12 deficiency:

9 had chromosome breaks

12 had abnormal chromosome # in some metaphases

### TABLE 1. Cytogenetic abnormalities

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date</th>
<th>Cytogenetic result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/91</td>
<td>46,XX[22] chromosome/chromatid breaks with random deletions [7] chromatid breaks with l(7;14)[1] 53,XX,+X,-2,+4,+8,+9,+10,+11,+13,+13,+16,-17,-18,+19,-22,-22,+3mar[1] 64,XX,+X,+3,+6,+8,+9,+11,+12,+12,+13,+13,+14,+15,+18,+19,+19,+22,+3mar[1] 65,XX,+X,+X,+1,+3,+5,+6,+7,+7,+8,+8,+8,+18,+18,+18,+18,+19,+19,+19,+22,+3mar[1] 10/91 Chromosome breakage study using diepoxybutane (DEB): DEB breakage rate — 0.08 breaks/cell (control range 0–0.10 breaks/cell) Spontaneous breakage rate — 0 breaks/cell</td>
</tr>
</tbody>
</table>

The number in brackets at the end of each karyotype indicates the number of cells with this karyotype.
CAN B12 REPLETION “GROW” LEUKEMIA?

**CASE:** 71 yoF developed B12 deficiency 5 years after hemicolecctomy (including ilium).

Marrow: megaloblastic anemia, normal karyotype, 3% blasts

**TX:** B12 1mg IM monthly → persistent cytopenias over next 3 mo

Marrow: 67% blasts, normal karyotype, consistent with AML

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Growth media + 100 mcg B12

631 colonies

Growth media

383 colonies

Two cases

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TREATMENT

Repletion

B12 1000 mcg IM daily x1wk
B12 1000 mcg weekly x4wk
B12 1000 mcg monthly maintenance

Check for…

… response?

… malignancy?

… polyglandular syndrome?

… what else is missing?
MAIN POINTS

1. B12 deficiency can have protean manifestations.
2. Plasma exchange is recommended for presumed TTP.
3. Look for LDH >3000, retics, and megaloblastic changes.
4. Treatment requires follow-up and monitoring.
5. Be aware of cognitive bias / “Necker Syndrome” and consider alternate possibilities.

Special thanks to Drs:
  Dan Martin
  Kara Walter
  Jennifer Vaughn
  Pam Becker
  Sindhu Cherian
CAN B12 REPLETION “DIFFERENTIATE” LEUKEMIA?

CASE: 57 yoF presented with pernicious anemia, low B12, 40% peripheral blasts.

% Peripheral Blood Blasts