The Deadly Hoover: A curiouser and curioser case of disappearing platelets

Rachael Starcher
The Deadly Hoover

A curiouser and curiouser case of disappearing platelets

Rachael W. Starcher, MD MA
Case Presentation

History of Present Illness

• 42 yo Male
• Symptoms x4 days PTA:
  • SOB with productive cough
  • Mouth pain
  • Epistaxis

Medical & Social History

• Tobacco use (10 pack-years)
• Methamphetamine (inhalational)
• Works on an apple orchard
• Exposed to chickens & dog
• Sprays pesticides
• Denies woodworking, metal working
• Lives in rural, north-central Oregon with no travel
Case Presentation

Physical Exam

- **HEENT**: poor dentition, gingival bleeding, dried blood near mouth and nose
- **Lungs**: crackles in the bases bilaterally
- **Lymph**: palpable, non-tender, mobile axillary and inguinal nodes bilaterally
Case Presentation

Initial Vitals & Labs

36.8°C, 104/64, **HR 97**, RR 16, 86% on RA - > 93% on 3L NC

- MCV: 93.6
- Eosinophils: **3.9** [0.0 – 0.5 \(10^9/L\)]
- Procalcitonin: **0.76**
- AST 132
- ALT 152
- Alk Phos 400

* (Baseline 0.9)
Summary

Problem list

- Thrombocytopenia (severe)
  - Spontaneous epistaxis
- Hypoxic respiratory failure (mild)
  - Pneumonitis
  - Bilateral ground glass opacities
- Eosinophilia (moderate)

- Normocytic anemia (mild)
- Hepatitis (mild)
- AKI (mild)
- Exfoliative dermatitis (mild)
- Tachycardia (mild)
- Lymphadenopathy
  - Axillary
  - Inguinal
“Would you tell me, please, which way I ought to go from here?”

“That depends a good deal on where you want to get to,” said the Cat.

-Alice and the Cheshire Cat

Alice’s Adventures in Wonderland
(Lewis Carroll)
Thrombocytopenia

**Decreased Production**
- Bone marrow
  - Failure
  - Suppression
  - Infiltration
- Myelodysplastic syndrome
- B12 and folate deficiency

**Sequestration**
- Splenomegaly
- PE
- Pulmonary HTN

**Increased Consumption**
- DIC/Sepsis
- Drug reaction
- HIT
- Alloimmune destruction (post-transfusion or post-transplantation)

**Multifactorial**
- Infections:
  - Viral
  - Rickettsial
  - Parasitic

**Autoimmune disease**
- Primary ITP
- Mechanical destruction
- TTP/HUS
**Hematologic Work-Up**

**FLOW CYTOMETRY REPORT**

**Collected:**
6/26/2020 00:00 PDT

**Received:**
6/26/2020 15:19 PDT

**Flow Cytometry Dx**

**BLOOD, FLOW CYTOMETRY:**
- No phenotypically abnormal B or T-cell population identified
- No blastic population seen by flow cytometry and morphology review

**OTHER:** (CD16) 7%; (CD56) 2%

**CYTOSPIN SLIDES:** Adequate

**INTERPRETATION:** Flow cytometry reveals mononuclear cells comprise 5% of gated cells. The CD3 positive population is less than 10% as a restriction. The CD3 positive population is phenotypically unremarkable. Flow cytometry gated on b5773 (22.5% of total). There is no circulating blasts or dysplastic cell lines.

Test results may not be reliable if the sample is collected with caution.

Note: This test was developed and its performance is approved by the U.S. Food and Drug Administration for clinical purposes. It should not be used as a substitute for gynecologic smear

Electronically signed by:
6/29/2020 12:10

**MYELOID MPN/MDS/CMML COMPREHENSIVE NGS PANEL, V2**

**REPORT SUMMARY**

0 Potentially Clinically-Relevant Findings

**Genomic Variant**

No clinically-actionable variants detected.

**ADDITIONAL INTERPRETATION**

No reportable variants in the MPN panel.

**FISH Analysis**

**Eosinophilia**

**Results:** Normal

**Interpretation:**
Normal results seen for the PDGFRA(q412), PDGFRB(q533), FGFR1(q11), and CEBPA(q22) probe sets.

Fluorescence in situ hybridization (FISH) analysis was performed using an eosinophilia probe set to detect abnormalities commonly associated with myeloid and lymphoid neoplasias with eosinophilia. All the signals were within the normal reference range. This represents a NORMAL result.

**Probe Set Detail:**
- PDGFRA(q412). The PDGFRA(q412) probe set shows a normal FISH signal pattern within the normal reference range.
Thrombocytopenia

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Primary (Idiopathic) ITP

Differs from secondary ITP caused by:
Malignancy, autoimmune diseases, drugs/toxins

Epidemiology
- Bimodal distribution (0-14 and >60 years)
- More common in females

Clinical manifestations
- Platelets worsen with transfusion
- Isolated thrombocytopenia
- Patients asymptomatic
- Improves with steroids, IVIG

Incidence of Primary ITP by Age and Gender

- Female
- Male

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence (per 100,000 per year)</th>
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<tbody>
<tr>
<td>0-14</td>
<td>4</td>
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<tr>
<td>15-39</td>
<td>2</td>
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<tr>
<td>40-59</td>
<td>3</td>
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<tr>
<td>&gt;60</td>
<td>5</td>
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“I can’t go back to yesterday, because I was a different person then.”

-Alice

Alice’s Adventures in Wonderland
(Lewis Carroll)
Complications Arise

Hospital Day 4

- Intraparenchymal, subarachnoid, and intraventricular hemorrhage
  - 1.1 cm midline shift
- Platelets <4 (10⁹/L)
  - Received 8 units pre- and intraoperatively
Platelet Trend

Severe spontaneous hemorrhage

- 1.5% of patients with <10k platelets
- Urgency of transfusion and treatment
Breakthrough!

“You should check for mercury poisoning…”
“Why, sometimes I've believed as many as six impossible things before breakfast.”

-Alice

*Alice’s Adventures in Wonderland*,
Lewis Carroll
Mercury Poisoning — The History

1819 - The first description of inhalational mercury poisoning.

1823 - Mercury touted as a cure for fevers.

1865 - "The mad hatter" depicted in Alice’s Adventures in Wonderland.

1951 - Disney releases first animated "mad hatter" to wide acclaim.

1956 - Minamata Bay, Japan: mercury in seafood identified as cause of mass death and disability.

2010 - Minamata Convention - 128 countries pledge to reduce mercury pollution by banning certain products by 2020.

2013 - Minamata (starring and produced by Johnny Depp) — docudrama to be released.

2021 - Johnny Depp’s Mad Hatter struggles with identity in delirium.
Mercury Poisoning

Background
• Most toxic non-radioactive metal in the world
• Found in the environment
• Main sources of exposure:
  • Eating contaminated seafood
  • Outgassing of dental amalgam
  • Occupational
    • Artisanal gold mining
    • Manufacturing
• 3 forms:
  • Metallic / elemental
  • Inorganic
  • Organic (does not respond to chelation)

Environmental Sources

Natural (e.g. volcanic, geothermal)
Remobilization (e.g. wildfires, biomass burning)
Pollutant (e.g. fossil fuel extraction, artisanal gold)
Mercury Poisoning

Routes of Exposure

- Ingestion
  - Intestinal necrosis
  - Hemorrhagic gastroenteritis
  - ATN or nephrotic syndrome
  - Erythema – “mad hatter disease”

- Transdermal
  - Hypersensitivity reactions
    - Erythema
    - Exfoliative dermatitis

- Inhalational
  - Rapid uptake, acute symptoms
  - Most dangerous exposure route
  - Acute pneumonitis
  - Erythema – “mad hatter disease”
Where did the platelets go?

**Thrombocytopenia & Mercury**

- Hematologic abnormalities present in 24% of cases of mercury poisoning
- Thrombocytopenia is a rare manifestation of mercury poisoning
  - Reported in only 0.23% of cases
  - Has a very high mortality rate

**Thrombocytopenia Outcomes**

- Survived: 24%
- Died from hemorrhage: 76%
Where did the platelets go?

Toxin-Induced ITP

- Many drugs have been implicated
- Studies compare effects of mercury to therapeutic gold
  - Both alter surface glycoproteins on platelets
  - Presented as antigens in Class II HLA immune response
  - Leads to anti-platelet immunoglobulin production & platelet destruction
- Mercury-induced ITP responds to chelation
  - Gold leads to chronic ITP
Rodent Autoimmunity

Rodent models

• Mice exhibit autoimmune type syndrome when exposed to mercury
  • Includes dose-dependent IgM, IgG, and IgE production
  • Induces ectopic lymphoid tissue
  • Frequently used as an animal model for autoimmune disease

• Relies on certain genetic susceptibility
Suspected genetic susceptibility

Genetic susceptibility → Autoimmune reaction

Autoimmune reaction → Lymphoid tissue
  ↓
  IgE

IgE → Eosinophilia

IgE → Anti-platelet Ig

Anti-platelet Ig → Thrombocytopenia

Lymphoid tissue → Lymphadenopathy
Mercury poisoning...?

- Aphas (from stroke) prevented patient history
- Family and friends not responding to contact
- Suspected inhalational and dermal exposure
  - Elemental mercury most likely
  - Responds to chelation

Do we chelate?

Patient Serum & Urinary Mercury Levels Compared to Normal Ranges

- Patient > 160
- Patient > 80

Patient Serum & Urinary Mercury Levels

- Normal 10
- Normal 5
Case Conclusion

Effects of chelation

- 30 days of chelation therapy
  - Mental status improved
- Platelets normalized
  - No evidence of chronic ITP

The rest of the story...

- Illegally purifying mined gold with mercury
- Spilled mercury and tried to clean it up
  - Covering his hands directly
- Vacuumed the spill from carpet
  - 12 case reports
  - Inhalational poisoning
Mercury rising

Impact of Climate Change

- Environmental mercury tripled over last 150 years
- Warmer water temperatures increase mercury concentrations in edible fish
- Forest fires release mercury previously safely stored in plant life
  - Oregon 2020 fires released 8x normal yearly pollution
  - Estimate 28% increase in wildfire emissions by 2050
Take Home Points

• Mercury poisoning is rare.
  • Most people think of “mad hatter’s disease”

• Toxin-associated ITP is exceedingly rare (0.23% incidence) but highly fatal.
  • Responds to ITP therapy and mercury chelation
  • Does not lead to chronic ITP

• Despite improvements in controlling mercury release, it is on the rise.
  • Driven in part by climate change

• Emphasizes importance of developing patient trust for hobby history
  • Secret and illegal hobbies could be the key when clinical picture doesn’t seem to fit

Extensive list of references available upon request