Occupational Environmental Toxicology Section Symposium
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Lessons in Metal Toxicity from Cases in an Occupational/Environmental Medicine clinic
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Case 1

- 52 yr old previously healthy man presented to ED with this hx:
  - several weeks feeling unusually tired
  - increased sleeping
  - Decreased appetite.
  - Sx’s worsened in the last week with significant aching in bones and flu-like illness leading him to remaining out of work the preceding week.
- Because of recent work (acetylene torching bridge beams and burning off paint) he requested blood lead be drawn
- ED PE unremarkable. Initial assessment: “stomach flu” and discharged home. BLL drawn.

Case 1

- Blood lead test returns 2 days later = 130 mcg/dL
- Normal LFT’s blood chemistries
- Hemoglobin 11
- Mental status and PE described as unremarkable
- He is admitted to a hospital for treatment
Case 1-hospital course

- Started on Ca-EDTA
- Within two days BLL was down to 64 mcg/dL and he was moved to the medical floor and transitioned to succimer, 700mg 3x per day only.
- New sx’s: slow speaking, confusion, agitation; more pain/aching back and calves
- BLL 63 mcg/dL; CT scan (no contrast)-negative; other blood work normal
- Venous US: normal and no clot
- Discharge 7 days later: BLL 24 mcg/dL, FEP 153

Case 1: Occ/Env Med consult
(1 wk after hospital discharge)

- Many sx’s: confusion, pain and achiness in leg bones and calves, intermittent band-like headache, nightmares (unusual), shakiness in hands (new), unbalanced when walking
- Still on succimer, 700mg twice per day
- BLL 2 days before: 30 mcg/dL
- PMH negative, except amputation/reattachment 2 fingers R hand; also partial severing right biceps tendon; Fully functional and strong afterwards
Case 1: Occ/Env Med consult (1 wk after hospital discharge)

- Meds: only succimer
- Cigarettes: 1PPD
- Alcohol or other drugs: denied

Case 1: Occupational History (per patient)

- Has been working as a skill carpenter and burner/cutter-no sx’s;
- 4 months previously hired for a new company, and had PPE: NORMAL; BLL test performed (“not available”), urine lead (10 mcg/gram creatinine); FEP (borderline above reference), Cadmium not elevated. Normal hemoglobin of 15.
- Subcontracted to work for another company: Use an acetylene type torch to burn off some paint form bridge/highway steel beams and then cut through the metal. Work done in the company yard, outside.
Case 1: Occupational Hx

- Fitted for cartridge respirator
- At job site, found to have incorrect filters, and given another (poorly fitting mask)
- Could taste and smell metal/paint, and saw paint chips in the mask.
- No work clothes or change of clothing
- Ate lunch in car-no place for hand washing before eating or smoking
- Denies other part time jobs or other environmental exposures
- ~2 weeks after start began feeling the fatigue symptoms

Case 1: OEM consult- PE

- Weight 144 lbs; BP 148/84
- HEENT: nl pupils, EOMs. Fair dentition, no lead line
- Lungs: clear; CVS: normal, no murmur
- ABD: diffusely, mildly tender; neg HSM
- Some Tender upper back, legs
- NEURO: Cran n 2-12 nl; MOTOR: gait unsteady and hard to walk heel-to-toe; strength (wrist extensors and grip) normal, but intention tremor, R>L; DTR’s nl; sens-light touch ok
Case 1: OEM consult- PE

• Mental status: appeared distress and concerned; MOCA—oriented to time, place, and picture naming, but problems with tests of executive function, attention and recent memory
• LABS:
  BLL=24; FEP= 204
  Other metals Mn, Hg, cobalt, chromium=within normal ref range
  CK normal (43)
  Low vit D = 23

Case 1: Initial Plan

• Given work note: Out of work (“Medical removal protection” per OSHA Lead standard)
• Advised company to assess its lead control measures
• Repeat BLL
• Follow up appointment, and reassess symptoms
Company responses

• Denied he had lead poisoning from them
  – First claimed he got it somewhere else
  – Then, that the beams were not lead painted
• Necessitated going to court
• Judge asks: how do you know you the paint
  had lead in it, and that he got lead poisoning
  from this job?

Case 1: Follow up

• Finished succimer course, then rebound BLL
• Worsening symptoms
  – Headache, skeletal/joint pain, tremor,
  – Worse cognitive problems
• Hospital readmission
  – Brain CT and MRI with no abnormalities
• Second round of chelation therapy with
  succimer (700mg twice per day x 2 weeks)
Case 1

- Continues out of work
- Prescribed PT/OT at home: denied by company
- No salary payment (no MRP)
- BLL after second chelation: 38 mcg/dL (3 months after d/c from initial hospitalization)
- Prescribed gabapentin for tremor and pain in his legs with some help

Case 1: 7-12 months later

- Extremely depressed because no income coming in AND because of persistent cognitive impairments (poor memory, organization, unable to drive)
- Continued weakness in legs
- No compensation to get OT/PT, and no treatment for the brain injury
- BLL's continue in the 20's
- Health insurance runs out after 1 year
- Neurobehavioral tests: many deficits, difficult to untangle from depression
Case 1 – Legal follow up

• Paint on beams assumed to be lead because taken from bridge with environmental impact statement noting presence of lead
• Legal resolution: given a settlement, but had to agree to no “blame or fault” to company
• Was supposed to have significant long term rehab—but stopped rehab stopped after 5 sessions
• Family continues to look for a rehab place that can do physical rehab in the setting of cognitive impairment

Case 1: 2 years later

• BLL persists in the teens (last one 3/2016= 13)
• Cognitive impairment—minimal improvement
• Continues with persistent leg pain and weakness
• Pain and tremor partially helped with gabapentin
• Continues to be very depressed by his cognitive and physical impairments and inability to work
• Continues on social security disability
Observations and “Take Aways”

• Acute severe lead poisoning can cause an encephalopathy in adults, and it may arise some days after finding of high BLL

• Sx’s of severe lead poisoning: headache, insomnia, mental confusion, severe joint pain; weakness wrists (extensors); +tremor much less common.

  (Hamilton A, Hardy H. "Industrial Toxicology", 1974)

• Note: normal liver function

• Persistent neurological sx’s and bone/joint pain

• Inadequacy of Worker Comp and Lead Standard
Case #2

HPI:

• 57 yo woman with h/o bilateral hip arthritis
• 10/2003 – Left total hip arthroplasty (THA), ceramic type-no problems
• 12/2004 – Right THA, ceramic on ceramic (CoC)
  – Revision in 6/2007 for mechanical failure
  – Replaced with metal ball in polyethylene cup (MoP)
  – No symptoms until July, 2014

Case #2

• June 2014 began having symptoms
  – difficulty walking /stairs with right leg
  – low grade fever, profound fatigue, headaches, rapid heart rate, and facial rash
  – No cough, no resp complaints, no myalgias
  – Lyme testing negative (x2), still treated with doxycycline

• September 2014 evaluated by Rheum for possible “muscle disorder”
  – Elevated ESR, CRP
  – Treated with 40 mg prednisone for few months
Case (cont.)

- Evaluated for dermatomyositis by Dermatology
- Diagnosed with hypothyroidism, started on Synthroid
- Decreased vision, decreased hearing, numb feeling hands and feet
- **Developed lumps on right leg**
  - MRI: anterolateral soft tissue swelling distal to the knee “extensive susceptibility artifact”
  - X-ray: “exuberant heterotopic bone formation”; no metallic foreign body
- Echo: mild concentric LVH, EF = 50%, trace AR, mild TR

Case (cont.)

- Saw orthopedist: Blood work performed (“blood” cobalt)
- Aspiration of right hip – “black like charcoal”
- Right THA revision on 1/26/2015
  - Metal rod in leg, totally ceramic hip joint
- Repeat testing performed

<table>
<thead>
<tr>
<th></th>
<th>Dec 2014</th>
<th>Jan 9 2015</th>
<th>Feb 12 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium (µg/L)</td>
<td>330</td>
<td>140</td>
<td>105.9</td>
</tr>
<tr>
<td>Cobalt (µg/L)</td>
<td>761</td>
<td>788.1</td>
<td>468.8</td>
</tr>
</tbody>
</table>
Refer to OEM Clinic 2/25/2015

• Current problems related to her high cobalt levels? Are they reversible?
  – Headache improved since hip replacement
  – “Brain fog” – hard to remember things
  – Numbness tingling feet
  – Persistent tachycardia
  – Underactive thyroid
  – DOE
    – Vision problems (“moderate cataracts”, “nonexudative macular degeneration”)
    – Hearing loss and tinnitus
    – Urinary urgency
• Should she be chelated to lower her Cobalt and chromium levels?
• Can she work (OOW since December 2014)

Status at OEM consult

• PMH and PSH:
  – Arthritis of the hips
  – C-section for her 5th child
• Occupational Hx:
  – Recycle coordinator
  – Former CNA nursing home
• Tobacco:
  – 1-1.5 ppd since 1970
  – quit 1/2015
• EtOH:
  – Rarely (<1/week)
• Medications:
  – gabapentin
  – levothyroxin
  – omeprazole
  – warfarin (now off)
• Herbal remedies: none
  – Tried clay to decrease cobalt and chromium
• Allergies: none
• Diet: vegan
Physical Exam

• VS: BP 118/70, HR 102
• Gen: walking with crutches, NAD
• Neck: thyroid not enlarged, no nodules
• Ext: healing incision right hip
  – firm discrete area of induration along right gastroc, no warmth or erythema
• Neuro:
  – Cerebellar testing with minimal endpoint tremor on FNF
  – Normal heel to shin
  – DTRs: absent at knee and ankle
  – Stocking/glove decrease PP
  – MS-unremarkable with normal interview

CHA Lab Testing

• Normal thyroid (on meds) and vitamin B12 levels
• Mild microcytic anemia
• Cobalt (plasma): 169.4 μg/L (ref: 0 – 0.9)
• Chromium: 156.4 μg/L (ref: 0.1 – 2.1)
Cobalt
An essential nutrient

• One stable isotope ($^{59}\text{Co}$)
• About 26 radioactive isotopes (e.g., $^{60}\text{Co}$, $^{57}\text{Co}$)
Cobalt Component of Vitamin B12

Adults need approximately 2.4 µg/day of vitamin B12


Natural Exposure

- Released into environment by weathering of rock and soil and human activity
- Found in the air, drinking water, and food.
  - Average concentration in ambient air is approximately 0.0004 µg/m³; higher levels detected in industrial areas
  - Average cobalt level in drinking water = 2 µg/L; values up to 107 µg/L have been reported
  - Average daily intake of cobalt from food is 5 to 40 µg/day.
  - Background level from NHANES (urine=mean .498 mcg/gr creat)
- Higher exposure may occur in the occupational setting, particularly in the hard metal industry.

ATSDR, 2004
Cobalt Toxicity

• Data from occupational exposures
  – Respiratory effects (interstitial lung disease, asthma)
  – Dermal effects (allergic eczema; low skin absorption)
  – Other effects
• Quebec poisoning by beer (1965-66)
  – Cobalt chloride added as foam agent
  – Cardiac myopathy
• Treatment to increase erythropoiesis
  – Treat anemia in ESRD
  – Prevent anemia associated with pregnancy
    (did not help, but found some cases of hypothyroidism)
Elimination of Cobalt

- Vitamin B12 not synthesized in human body
- Cobalt is not metabolized
- Mainly urine excretion; also feces
- Excretion: multi-compartmental model: Rapid initial phase (about 30% first 24 hours), then up to 73% in 48 hours, and about 57% within 2 weeks. Minor fraction, years-can be retained for years in liver.

CDC Biomonitoring Summary:
https://www.cdc.gov/biomonitoring/Cobalt_BiomonitoringSummary.html

Cobalt and Hip Replacements
Hip Replacement in the U.S.

5 Options:
- Metal-on-Metal
- Metal-on-Polyethylene
- Ceramic-on-Ceramic
- Ceramic-on-Polyethylene
- Ceramic-on-Metal


Metal-on-Metal Hip Replacement

- Cobalt-chromium-molybdenum alloy one of most common implant materials
- Used since 1939
- Resistance to corrosion
- Early reports of hypersensitivity leading to delayed implant failure

FDA. Metal on Metal Hip Implants
Coleman et al. (1973)
Early Research

- Increase metallic ions around implants in animal studies (Ferguson et al., 1960)
- Cobalt and Chromium found in blood and urine after THA with MoM and MoP (Coleman et al, 1973)
- 1975 first report of Cobalt toxicity following hip replacement
- Co and Cr levels as indicators for wear rates and performance of prosthetic joint

Revision of Failed Ceramic THA

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Revised</th>
<th>Time to Symptoms</th>
<th>Peak Co (µg/L)</th>
<th>Persistent Sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizzetti et al.</td>
<td>C?</td>
<td>MoP</td>
<td>2 mo</td>
<td>549 (B)</td>
<td>Partial visual loss</td>
</tr>
<tr>
<td>Oldenburg et al.</td>
<td>CoP</td>
<td>MoP</td>
<td>3 mo</td>
<td>625 (B)</td>
<td>Neurological symptoms</td>
</tr>
<tr>
<td>Ikeda et al.</td>
<td>CoC</td>
<td>MoP</td>
<td>2 yrs</td>
<td>&gt;400 (B)</td>
<td>Mild hearing loss</td>
</tr>
<tr>
<td>Steens et al.</td>
<td>CoC</td>
<td>MoC</td>
<td>2 yrs</td>
<td>398 (S)</td>
<td>Decreased visual acuity</td>
</tr>
<tr>
<td>Pelclova et al.</td>
<td>CoC</td>
<td>MoP</td>
<td>14 yrs</td>
<td>506 (S)</td>
<td>Pronounced hearing loss</td>
</tr>
<tr>
<td>Zywiel et al.</td>
<td>CoC</td>
<td>MoP</td>
<td>6 mo</td>
<td>6521 (S)</td>
<td>Fatal CM</td>
</tr>
<tr>
<td><strong>Current case</strong></td>
<td>CoC</td>
<td>MoP</td>
<td>7 yrs</td>
<td>788.1 (B)</td>
<td>Neurological symptoms, aches, decreased swelling</td>
</tr>
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- All had auditory symptoms (hearing loss or tinnitus)
- All but 1 case reported hypothyroidism and polyneuropathy
- Common: hip pain, weakness/fatigue, visual complaints, and cardiac abnormalities

Modified from Zywiel et al. (2013)
### Symptoms reported in Prosthetic Hip related cobalt toxicity patients

- Cardiomyopathy
- Hypothyroidism
- Peripheral neuropathy
- Hearing loss
- Fatigue
- Headache
- Cognitive impairment
- Vision problems (optic nerve atrophy, macular problems)
- Dyspnea


### Decisions: Case with Extremely High levels of Cobalt

- **Systemic toxicity:** are her symptoms consistent with cobalt poisoning?
  - **YES:** New onset of symptoms of hearing loss, thyroid dysfunction, peripheral neuropathy, retinal damage, tachycardia, (possible, mild) cardiac myopathy at time of elevated levels of Cobalt—very consistent
- **What treatment? Should she be chelated?**
Chelation therapy for cobalt poisoning from the metal hip degeneration

- First line of treatment: HIP REPLACEMENT—remove the source!
- Very limited data on value of chelation:
  - One case treated with Ca-EDTA, reduced whole blood cobalt, then rebound
  - I had concerns about increased levels in heart
  - No difference in brain cobalt, treated and untreated animals


Case 2: Decision making

- Is there further treatment, and one that might make my symptoms better (Chelation?, dialysis) NO
- Will her symptoms get better when the cobalt levels go down? [more info on thyroid, but little on other symptoms]
- PLAN:
  - Continue to monitor, particularly thyroid
  - Out of work
Further follow up: Case 2

• Follow up appt March, 2015:
  – Repeat blood cobalt higher (282.9)
    468.8 to 282.9 (over the month)
  – Different lab through CHA (plasma)
    164.4 to 123 mcg/L (ref 0.0-0.9)

Case 2—July, 2016

• Follow up blood cobalt levels:
  – 3/2015 = 180 mcg/L (another lab)
  – 9/2015 = 62.1 mcg/L
  – 3/2016 = 43.1
• Chromium continue in the 100’s.
Case 2 – July, 2016

• Hearing: has hearing aides, but thinks improving—may get retested
• Thyroid function normalized, off supplemental thyroid since 4/2016
• Heart rate better now 90’s
• Vision: to have cataract surgery in August, 2016
• Peripheral neuropathy—not much improvement
• Also double “frozen shoulder”? Relate to cobalt or separate problem?

Some lessons
Measurement of Cobalt may vary depending on source

- Importance of proper collecting tube (acid washed, metallic free)
- *Whole blood* (tube with EDTA to prevent clotting (eg Quest))
- *Plasma*: EDTA, but quickly remove liquid (plasma level)—contains clotting factors (eg LabCorp)
- *Serum*, allow blood to clot, then remove supernatant, “serum” ~ no plasminogen or clotting factors

Serum vs. Plasma vs. Whole Blood

- Pay attention to units, and also media: blood, or plasma, or serum?
- Generally good correlation between serum and blood, but may not be the same
- If comparing, or following over time, be consistent
General Approach to Decision Making
Milder elevated levels

- Assessment and interpretation of the biological monitoring test
- Relationship of the biological test result of cobalt to the status of the hip integrity and function
- Relationship of the biological test result of cobalt to the potential or presence of systemic toxicity

Decision making for other cases of modestly elevated cobalt

- What about the person with a blood (or plasma) cobalt 10ug/dL-20ug/dL
- Any hip symptoms?
- Risk stratification algorithm—focus on the hip status

**TABLE II MoM ‘Low Risk Group’**

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<th>'Low' Risk Group Stratification</th>
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<td><strong>Treatment recommendation</strong></td>
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**TABLE III MoM ‘Moderate’ Risk Group**

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What about elevated cobalt and NO HIP SYMPTOMS

- Blood cobalt levels that are elevated, but the person has NO SYMPTOMS
- Little or no data about long term systemic toxicity
- Need to weigh risks of hip replacement/revision surgery vs. potential long term risks
- Role of toxicologist/OEM specialist: keep up with the literature, communicate with patient
Summary

- Consider cobalt toxicity in patients who have had THR and present with signs of neuro-ocular, cardiac, and thyroid toxicity (NEJM case of missed cobalt toxicity in person with hip replacement
- Not just a problem of MoM THA
- No clear dose-response understanding of cobalt toxicity, especially for chronic toxicity
- Still evolving what symptoms and injury will be reversible
- Good correlation between serum and whole blood; whole blood may be preferred because more stable
- Should use same lab for comparisons or serial

Good References

- ATSDR – Cobalt, 2004
Case #3: Untangling a complicated case

• 56 yo man saw new PCP 11/24/2015
• Lab screen: Hgb 14.0, MCV 66.7, aniso, ovalocytes, target cells, hypochromia; FE, TIBC, iron saturation (30%), ferritin and folate
• NL Chemistries but BUN 22, Creatinine 1.27, eGFR slightly low 58.9 (ref >= 60).
• 12/21/2015: Hgb 13.4
• 12/21/2016: Rx HTN; nl screen chest CT scan (cigarette smoker); persistent microcytic anemia
• Referred to hematology
Case #3

- Hematology consultation 2/2016, w/u:
  - Hgb 13.1, MCV 65.1
  - HGB electrophoresis: high Hgb F (11.7%)
  - NI LDH
  - Lead (as screen) = 54 mcg/dL
  - Patient told to reduce exposure to lead dust (may occur as transporting jewelry mfg’ed with lead metal)
- Follow up Heme consult, 5/2016: microcytosis continues
  - Decides to Refer for OEM consult
  - Was lead the cause, or making his microcytic anemia
  - Should he be chelated?

Case #3: OEM consultation
(7/22/2016)

- Symptoms:
  - Only fatigue and difficulty sleeping (but has a number of situational worries)
  - Denies HA, difficulty concentrating, abdominal pain, constipation; Also, no black stools
Work History

- Job Title: jewelry salesman
- Since 1978: arranges and supervises the creation of the jewelry at different stages, and different locations, finally bringing to a purchaser for sale. He does a lot of travel
- Higher end products sue only silver and gold; cheaper products made using lead (sometimes as much as 30-50%), also cadmium and antimony.

Work History

- Last 10 years going to places where cheaper metal jewelry being made
- Goes into shops with lead dust, possible lead fumes (mold release powder with adherent lead). Carries and opens dusty boxes containing the jewelry
- No respirator; no change of clothes; smokes and eats in car
- After getting BLL result, decreased his handling of boxes, but still going to those work areas
Medical History

• Medical: Anemia; high cholesterol; HTN
  Chronic back issues

• Hospitalized 2005 for diverticulitis, s/p colostomy
  with reversal 2005; told he also had “cysts” on
  kidneys

• Cigarettes: ½ PPD x 29 years

• ETOH: < 1 drink per week

• Allergies: none

• Meds: Percocet 5-325 2x per day as needed for
  back; Ramipril 2.5/d; pravastatin

Family History

• Father died 76: Heart disease, DVT, Cystic kidneys

• Mother (smoker) died 75, COPD, asthma, arthritis

• Multiple paternal aunts with cystic kidneys
  (ESRD), one with transplant; All 8 siblings with
  polycystic kidney disease

• 3 sister and 1 B with thalassemia (or ? Thal trait)

• 2 daughters live with him (separated x 10 years)
Physical Exam

- VS: Wt 119 lbs; BP 110/74; Ht 67”; BMI 24.1, RR=16, P=82, pulse ox= 99
- HEENT: normal and no lead line
- Chest: clear Lungs
- CVS: regular rate, nl HS, no murumur
- Abd: non tender; no masses; neg HSM
- Ext –normal-no edema
- Neuro: Cran N 2-12 nl; Full strength, proximal and distal; normal gait, FTN, HTS, neg Romberg; can walk heel to toe; DTR’s 2+= UE, KJ; AJ=1+,=; MS normal

CHA LABs

- Hgb = 13.0, MCV 65.8, smear moderate high Burr cells, slight target, anisocytosis
- Fe=86, ferritin 96 (26-388)
- BUN= 22, creatinine 1.4 (high), eGFR=52
- LFT’s = Normal ranges
- Lead = 57 mcg/dL; FEP =89 (0-34); ZPP=98 (0-38)
- Cadmium (blood) =5.9 (0-1.2) mcg/L
  Cadmium (urine) =1.6 mcg/gram creatinine
- Antimony, none detected
Problem List

• High BLL—no clinical symptoms. Is this the cause of his microcytosis?
• Microcytic Anemia – May have thalassemia trait, and not Fe def. Is there a contribution from lead?
• Mild kidney impairment, probable polycystic kidneys: is there a contribution from lead?