Clinical Problem-Solving (CPS) Case

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Management of the Hospitalized Patient
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Ground Rules for CPS Exercise

• Goop has never heard this case
  – Not a trivial undertaking
• Goal is to make the thought process of a master clinician transparent
  – It’s not magic
  – You don’t have to “know everything”
• “Getting it right” is cool, but relatively unimportant in the grand scheme
• Have fun: this is why many of us went into medicine
Clinical History

**CC**: A 41 year-old man of Indian (South-East Asian) descent presents with 6 months of fever and weight loss.

**HPI**: The patient was well until approximately 6 months ago, when he noted the onset of fevers. The fevers began with flu-like symptoms, including a dry cough and achiness. The first episode lasted about a month, then went away without treatment.

Clinical History II

**HPI (continued)**: Subsequent episodes have come on approximately once a month. They generally last for approximately 7-10 days, then may abate for a week or two, and then start up again. He has noticed poor appetite, and a weight loss of approximately 12 pounds over the period, though his weight has been steady over the past month.

Review of Systems

- **Positive for**: night sweats, some joint pain (mostly right leg and low back both midline and over hips) only with fevers; headaches (back of head and behind eyes), also usually with fevers; extreme fatigue. Mild dry cough at first, minimal nausea – neither remain prominent Sxs

- **Denies**: skin rash, visual changes, URI sxs, stiff neck, chest pain, light headedness, SOB, hemoptysis, abd pain, diarrhea, constipation, blood in urine or stool, joint swelling, any neurological symptoms except headaches.
Goop’s Initial Thoughts

Past History/Family History
- Mild "prostatitis" x 5 years with difficulty urinating
- Mild vitiligo x 1 year
- Hx of 2 cm ASD seen on echo a year ago
- s/p Appendectomy, age 7
- History of positive PPD, BCG status unknown
- Meds: He has tried Motrin and Tylenol, which helped with fevers
- FH: Father with DM and CAD. Older brother with heart defect, died age 32 following heart surgery

Social History
- Patient born in Southwest US, family from Mumbai, now lives near his hometown in US
- Former smoker, quit 1995
- Drinks few glasses wine/week
- Works as investment advisor; frequent travel to India, Asia. Most recent trip was to India, about 1 month before sx began
- Had illness with fevers, bilateral diffuse joint aches after trip to Taiwan 2003, resolved
- Two healthy children, ages 9 and 11
- Has a dog but no other pets
Prior Medical Care

- By report, exam and labs done over past few months in PCP’s office were “unremarkable.” Actual w/u not clear, results pending.
- Referred two weeks ago to university hospital, seen in ID clinic.
- W/u there included ESR of 25 and a positive quantiFERON gold. Not yet begun on INH, but “we will probably do it next visit.”
- Started in ID clinic on Doxycycline (unclear indication), no change in symptoms since starting.

What is Your Initial “Hit” on the Case?

1. An infection
2. A tumor
3. A metabolic/electrolyte abnormality
4. A medication effect
5. A rheumatologic disease
6. Something else
Physical Examination I

- VS: T 37 BP: 100/60 HR: 83 RR: 16
  O2 sat: 99% RA
- General: Thin man in no acute distress
- HEENT: NCAT, EOMI, PERRL, no oral lesions
- Neck: supple, no LAN
- CV: NSR; no m/g/r
- Chest: CTAB
- Abd: soft, non-tender, non-distended, no HSM
- Extremities: No CCE, no adenopathy
- Neurological: A&Ox3, CNs intact, no focal deficits

Initial Labs

139 102 11
3.8 27 0.92

Anion Gap: 10
Glucose: 91
Ca: 9.2  TP: 7.7  Alb: 3.9
Alk Phos: 183  AST: 54  ALT: 59
Bili: 0.7

Initial Labs (cont’d)

3.6 41.7 152

55% polys; 31% lymphs; 11% monos; 1.3% retics
UA: negative
CXR: negative
BC’s x 2: negative
Now I’m worried about…

1. Tuberculosis
2. Endocarditis
3. Another chronic bacterial infection
4. Malaria
5. A hematologic malignancy
6. A vasculitis
7. Factitious fever
8. Something else

I’d order the following studies

1. Echo and more blood cultures
2. Head/Spine MRI and blood smear
3. Sputum AFB and repeat quantiFERON gold
4. HIV test
5. Thick and thin blood preps
6. ANA, ANCA, anti-Smith, and serum complements
7. Something else
Next Steps

• The physicians ordered more blood tests…
  – CRP 2.8, Toxo (neg), Ferritin 1936, LDH 622
• …and a peripheral smear:
  – Normocytic, normochromic red cells with mild
    anisocytosis and poikilocytosis. Moderate
    number of variant lymphocytes seen
• … and an MRI of brain and spine:
  – “Hyperintense signal diffusely through C-spine,
    L-spine, and sacrum, suggesting marrow
    infiltrative process”

What Would You Do Now?

1. Bone marrow biopsy alone
2. Bone marrow biopsy plus start TB
   treatment with four drugs
3. Bone marrow biopsy plus abd/pelvic CT
4. Bone marrow biopsy plus start
   antimalarials
5. I wouldn’t do a bone marrow biopsy (I
   agree to voluntarily relinquish my board
   certification on the way out today)
ID F/u Visit

- Additional history obtained:
  - 2003 illness called "Chikungunya-like" by ID doc (not clear if he was just showing off)
  - More travel/exposure hx: "hikes frequently, inc. cabin stays," frequent business trips to India/SE Asia: no prophylaxis. Drank filtered water, milk from commercial vendors, ate raw meat/fish (sushi, steak tartare). No sexual contacts with new partners, IVDU, transfusions while traveling
  - Tracked down prior PCP w/u, including abd-pelvic CT: mild retroperitoneal nodes only

A Bone Marrow Aspirate/Biopsy Was Performed

- Hypocellular marrow
- No granulomas seen
- Mild “reactive process”
- No AFBs, cultures negative
- No malignancy seen on cytology, flow, or karyotype studies
What Would You Do Now?

1. Start TB treatment
2. Start malaria treatment
3. Repeat the pan-CT scan
4. PET scan
5. Admit the patient to the hospital for an old-fashioned FUO work-up (remember those?)
6. Watchful waiting

Hospital Admission

- Prompted partly by a pre-syncopal episode, the patient was admitted
- CBC now with Hct 32, WBC 2460 (ANC 1800), Plts 35. IL-2 receptor 2931 pg/ml
- Temp up to 40 on several occasions
- No N/V/diarrhea, abd pain, joint pain
- Does note mild h/a with fevers
- Heme consult: “c/w hemophagocytic lymphohistiocytosis”: fever, cytopenia, high ferritin, high soluble IL-2 (4/8 criteria)
  - Rest: splenomegaly, hyperTG or hypofibrinogenemia, hemophagocytosis on BM/smear, low NK-cell activity

Started on Rx for Macrophage-Activating Syndrome

- “The patient’s inflammation-driven systemic process appears progressive and immunosuppressive therapy is warranted.”
  - Dexamethasone 20 mg/d
  - Cyclosporin 300 bid
  - PCP and TB prophylaxis (Bactrim, INH)
- Some improvement in fever curve
- Repeat CT scan: new splenic lesions concerning for abscesses
At this point, I’d…

1. Start the patient on four-drug TB therapy and stop the steroids/cyclosporine
2. Start the patient on four-drug TB therapy and continue the immunosuppressives
3. Start the patient on broad spectrum Abx and stop the immunosuppressives
4. Start the patient on Abx, antifungals, and TB Rx and stop the immunosuppressives
5. Do a splenic aspirate
6. Perform a splenectomy
7. Repeat the bone marrow studies
8. Perform an LP

Hospital Course, cont.

• Treatment for hemophagocytic lymphohistiocytosis discontinued when CT results became available
• Four-drug treatment for TB was begun
• Patient continued to spike up to 41 degrees daily for 4-5 more days
• A diagnostic procedure was performed
Repeat Bone Marrow

- Hypercellular marrow
- Necrotizing granulomas, AFB negative
- Atypical lymphoid infiltrate with EBV positive Reed-Sternberg-like cells c/w classical Hodgkin Lymphoma
- Hemophagocytosis present

Subsequent Course

- PET scan: c/w diffuse lymphoma predominantly osseous, splenic involvement present
- Patient underwent splenectomy, which demonstrated Hodgkin’s Disease
- Started on chemotherapy
- TB treatment discontinued
- In f/u (short-term), fevers resolved, doing well
Summary

- 41-year old American man of Indian descent with prolonged fevers found to have Hodgkin’s lymphoma
- Diagnosis made on repeat bone marrow biopsy after initial one was negative

A Cautionary Tale

In an era in which waste reduction is an increasingly prevalent mantra, it is important to think about the test characteristics and the post-test odds and consider repeating tests, particularly ones with low risk

Repeat Testing as a Marker of Waste

No Option for “Low Sensitivity Test in Patient with Life-Threatening Disease”
“The emphasis must be on careful, repeated, and frequent examination of the patient…”

Pre-test odds=40%; Likelihood ratio~0.4 (BM ~60% sensitive), then...

Post-test odds=18%

“Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth.”

-- Arthur Conan Doyle