Splenomegaly in Congolese Refugees: Common and complicated

William Stauffer MD
(Laura Zambrano PhD, MPH, EIS Officer)
Professor, University of Minnesota
Medical advisor, IRMB, DGMQ, CDC
• Perspectives provided are my opinion only and are not necessarily those of the CDC

• No financial disclosures but 3 disclaimers
Disclaimer #1: I am a clinician primarily
Disclaimer #2: I use the word “We” a lot...most the actual work is not me...
Disclaimer #3
I know less than when I started about splenomegaly
If I am successful, so will you 😊
Case Scenario

- 15 y/o Ethiopian female referred from pediatric heme/onc for enlarged spleen. Extensive heme/onc evaluation negative (excluding bone marrow bx).

- ID question, is this infectious?
15 y/o Ethiopian female with a large spleen

HPI

- Patient immigrated from Kenya 14 months previous. Reports “feeling hot”: tactile fevers? Originally from southern Ethiopia (near Awassa)

- Abdominal discomfort…fullness.

- No weight loss or night sweats but weakness and fatigue, difficulty with walking one block.

- Uncle states she has had “a big stomach since she was ~5 years of age”
15 y/o Ethiopian female with a large spleen

- Physical Examination
  - VSS, afebrile
  - RRR, flow murmur
  - CTA B
  - Abd +BS, Right palpable mass/spleen to umbilicus and to left pelvic gutter, uncomfortable but not tender. Liver 7 cm in span
15 y/o Ethiopian female with a large spleen

- **Laboratory**
  - WBC 1.1 (N abs: 700, L 400)
  - Hgb 8 (MCV 78)
  - Platelets 21
  - LFT's normal

- **CT:**
Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- 23 yo Ethiopian male with 3-4 weeks of drenching fevers
- Migrant, working in sorghum fields in NW corner (near Sudan) of Ethiopia
- Daily nose bleeds
- Very weak, ambulatory (but barely), lost ~9 kg over last month
- Similar presentation 1 year ago, treated at MSF with daily injections and got better

Special Thanks: Ann Settgast for case
Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- **Physical Examination**
  - Cachectic (BMI 12), Temp 101
  - O/P dried blood
  - Abdomen grossly enlarged (and visible) spleen
  - Epitrochlear and inguinal LAD

- **Laboratory**
  - Rapid malaria test negative; Hbg 7.6
Case 3: 7 yo Congolese male with “stone” in abdomen

- 7 yo Congolese male being screened for US refugee resettlement
  - Living outside Hoima, Uganda
  - Migrated to Uganda when 4 years old
  - Asymptomatic, but when asked, his parents say he has a “stone”
Case 3: 7 yo Congolese male with “stone” in abdomen

Physical Examination
- Normal except for abdomen—liver span normal, spleen grossly enlarged, uncomfortable with palpation

Labs
- Hgb 10; Plts 125, WBC 4.3
- Rapid malaria test negative
Differential diagnosis (in particular, tropical infections)?
Splenomegaly
**Splenic Function**

- Clearance of microorganisms and antigens
- Synthesis of immunoglobulin G (properdin)
- Removal of RBCs
- Extramedullary hematopoiesis
Differential diagnosis—by mechanism

- Immune response
  - Infection (endocarditis, mononucleosis)
- RBC destruction leading to hypertrophy
  - Hereditary spherocytosis or thalassemia’s (major)
- Congestion
  - Splenic vein thrombosis
  - Portal hypertension
- Neoplasms
  - E.g. leukemia/lymphoma
- Myeloproloferative
  - Chronic myeloid metaplasia
- Infiltrative
  - Sarcoidosis, Gauchers, amyloidosis
- Misc
  - Structural
    - Cysts
    - Hemangiomas
    - Metastasis
    - Abscess (giant)
    - Drugs (RhoGam)/Toxins
    - Etc…
Tropical Differential Diagnosis (top four I think about first)

- Malaria
- Schistosomiasis (mainly liver disease sequelae, can be immune mediated)
- Visceral Leishmaniasis
- Brucellosis, (any common cause of chronic liver disease (e.g. viral chronic hepatitis, toxins), TB?)
Schistosomiasis

- Epidemiology
  - Endemic in 74 countries
  - 600-800 million at risk, ~200 infected, ~120 symptomatic, ~20 million with severe disease
  - 85% in Africa
Species

Intestinal
- S. mansoni
- S. japonicum
- S. mekongi
- S. intercalatum

Urinary
- S. Haematobium

Rare Zoonotic
- S. bovis
- S. mattheei
- S. margrebowiei
- S. curassoni
- S. rodhaini
90% in six countries: Bangladesh, Brazil, Ethiopia, India, Sudan, South Sudan

*L. donovani* and *L. infantum* and affects internal organs (particularly, spleen, liver, and bone marrow).
Leishmaniasis (Visceral)
Leishmaniasis (Visceral)

- Kala-azar (“black fever” in Hindi)

- **Typical symptoms**
  - fever
  - weight loss (cachexia; wasting)
  - hepatosplenomegaly (usually, the spleen is more prominent than the liver)
  - pancytopenia—i.e. anemia, leukopenia, and thrombocytopenia
  - a high total protein level and a low albumin level, with hypergammaglobulinemia
Diagnostic evaluation?
Non-clinicians: you can Go to your happy place
15 yo Ethiopian female with splenomegaly

**Most pertinent test results**

**Liver CT normal, LFTs normal**

- Malaria
  - Peripheral smear negative
  - RDT *(weak positive for non-falciparum—aldolase; negative for falciparum—HSP1)*
  - Malaria serology (IgG negative); Total IGM slightly high
  - Malaria PCR negative

- Schistosomiasis
  - Stool ova and parasite *(S. mansoni ova in 1/3 —H. nana 1/3)*
  - Schistosomiasis serology negative

- Leishmaniasis serology negative
- Other serologies negative: brucella, hep B and C, EBV
15 yo Ethiopian female with splenomegaly

What do you think the most likely diagnosis is?

A. Malaria (hyper-reactive splenomegaly syndrome
B. Schistosomiasis
C. Visceral Leishmaniasis
D. Brucellosis

Reminder:

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  - Stool ova and parasite (*S. mansoni* ova in 1/3 — *H. nana* 1/3)
  - Schistosomiasis serology negative (call from outside lab, positive)
Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

Most Likely Diagnosis?

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DAT +, HIV +
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- A few learning points
  - Highly geographically determined (as with most infectious diseases, but even more so...)
  - Description of sodium stibogluconate--hint (30 days IM)
  - Recurrence: hint for HIV
  - Epistasis is very common (amastigotes replace BM causing thrombocytopenia)
  - Epitrochlear nodes very common
Case 3: 7 yo Congolese male with “stone” in abdomen

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Most Likely Diagnosis?

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C. Visceral Leishmaniasis
D. Brucellosis
Splenomegaly among Congolese refugees from Uganda
Investigation Context

- Kyangwali Refugee Settlement:
  - Hoima, Uganda
  - Most refugees are from DRC
  - Higher than expected number of splenomegaly cases
Evaluation

- With assistance of CDC, IOM implemented a diagnostic and treatment protocol:
  - Additional screening and diagnostic testing
  - Questionnaire, Survey data
  - Ultrasonography
  - Treatment
Clinically Palpable Spleen

Overall protocol: First Encounter, Initial Medical Exam ~3-6 months prior to departure

- Initial Health Assessment (Time 0)
- At Departure (Generally 3-6 months later)
- On U.S. Arrival (1-2 months after departure)

Abdominal Ultrasound

Laboratory Testing (point-of-care)

Serology

Pre-departure presumptive therapy and repeat laboratory testing, ultrasound

Post arrival screening data (malaria serology and repeat ultrasound)
Splenomegaly

Laboratory Testing (Blood)
- CBC with diff & platelets
- LFT's (AST, ALT, Bilirubin, PT/INR, Alk phosphotase)
- Rapid malaria test (falciparum & non-falciparum)
- Thin blood smear for malaria
- Hepatitis B and C testing
- Rk39 for Leishmaniasis
- HIV testing

Laboratory Testing (Stool and Urine)
- Stool ova & parasite (x3)
- Urine ova and parasite

Positive results: Treated according to Uganda National Guidelines

Record all results on DS Form
Procedure at Departure (all refugees)

**Routine Presumptive Treatment**
- Praziquantel
- Albendazole
- Co-artem

**Additional Testing (as indicated,)**
- Malaria Serologies
- Repeat ultrasound (measurements)
- Other testing as clinically indicated

**Tracking system:**
Notify states and provide written treatment advice and/or clinical consultation
RK39 (amastigote antigen)

The test is considered positive with the appearance of two red lines (one in the control area and another in the test area). The test is considered negative with the appearance of a single red line in the control area.
Perceptions in local communities

Splenomegaly is a well known

There is a name in all the major language local languages

“Ekibaare” in local language (Runyakitara) which can be literally translated in English as a “big stone”
It is perceived as:

- Non-fatal
- Mainly a childhood illness
- Associated with malaria
- Not routinely associated with witchcraft
- Treated traditionally with herbs or through traditional practices (pictures to come)
Local Care:

- Unlikely to seek medical care

- Some clinicians treat using a weekly dose of quinine for 6 months.

- Rarely clinically investigated beyond malaria testing Hb estimation.
Results

- Refugees: 145/987 (14.7%)
  - Signs/Symptoms
    - 85% massive, 14% moderate, 1.4% mild
    - >98% born in Congo, clustered in families
Splenomegaly cases by age group

- < 5: 0.7%
- 5-11: 25.5%
- 12-17: 37.9%
- 18-39: 24.1%
- 40-60: 10.3%
- 60+: 1.4%

Age in years: 0, 10, 20, 30, 40, 50, 60
<table>
<thead>
<tr>
<th>Test</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Hemogram</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia (Hb &lt;12 g/dl)</td>
<td>82 (57.3)</td>
</tr>
<tr>
<td>Leucopenia (WBC&lt;4)</td>
<td>23 (15.9)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150,000)</td>
<td>55 (37.9)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>14 (9.7)</td>
</tr>
<tr>
<td><strong>Ova for Schistosoma mansoni</strong></td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Leischmaniasis Antibody test</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td><strong>Rapid Diagnostic Test for HIV</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>143 (98.6)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td><strong>Malaria RDT positive</strong></td>
<td>39 (26.9)</td>
</tr>
<tr>
<td><strong>Hepatitis B surface Antigen positive</strong></td>
<td>5 (3.5)</td>
</tr>
</tbody>
</table>
Splenomegaly post-arrival

Post-arrival management

- Test for G6PD, treat with Primaquine x 2 weeks
- Repeat ultrasound and monitoring of splenomegaly and any associated abnormalities (e.g. hematologic abnormalities)
- Avoid contact sports or activities place at risk for abdominal trauma
- CDC clinical assistance in management and follow-up
Last few words on “Hyperreactive Malarial Syndrome”

- Common manifestation of repeated malarial infections
  - Familial clustering, potential genetic predisposition
  - Prevalence ranges 0.16% (Gambia) to 80% (PNG)
    - Pathogenesis poorly understood, largely immune mediated..
Hyperreactive Malarial Syndrome


<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N patients</th>
<th>Type of treatment</th>
<th>Duration</th>
<th>Follow up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior 1967 [49]</td>
<td>New Guinea</td>
<td>99</td>
<td>CLQ 1500 mg/3 days, then 300 mg/wk</td>
<td>NR</td>
<td>average 4.1 mths in hospital plus 6-23 mths out</td>
<td>No change in spleen size, general benefit</td>
</tr>
<tr>
<td>Sagoe 1970 [57]</td>
<td>Nigeria</td>
<td>43</td>
<td>PG 100 mg /day</td>
<td>≥6 mths</td>
<td>6 mths</td>
<td>32 improved 11 worsened</td>
</tr>
<tr>
<td>Stuvier 1971 [27]</td>
<td>India</td>
<td>14</td>
<td>PQ 15 days, then CLQ 300 mg/wk</td>
<td>6-14 mths</td>
<td>once/mths for ≥6 mths</td>
<td>11/14 spleen size ↓50%</td>
</tr>
<tr>
<td>Stuvier 1974 [71]</td>
<td>Uganda</td>
<td>41</td>
<td>CLQ 300 mg/wk or PG 100 mg /day</td>
<td>NR</td>
<td>4-20 mths</td>
<td>all improved</td>
</tr>
<tr>
<td>Bryceson 1976 [60]</td>
<td>North Nigeria</td>
<td>30</td>
<td>PG 100 mg /day</td>
<td>3 - 12 mths</td>
<td>3 mths</td>
<td>12/13 improved (17 lost)</td>
</tr>
<tr>
<td>Fakulle 1980 [64]</td>
<td>Nigeria</td>
<td>69</td>
<td>PG 100 mg /day</td>
<td>3 mths</td>
<td>10 wks</td>
<td>2/40 died plus 8/29 defaults</td>
</tr>
<tr>
<td>De Cock 1986 [52]</td>
<td>Kenya</td>
<td>38</td>
<td>PG 100 mg /day or CLQ 300 mg/wk</td>
<td>NR</td>
<td>NR</td>
<td>13/18 improved (20 lost)</td>
</tr>
<tr>
<td>Crane 1986 [2]</td>
<td>Papua NG</td>
<td>148</td>
<td>CLQ 300 mg/wk</td>
<td>lifelong</td>
<td>12-18 mths</td>
<td>146 improved (2 lost)</td>
</tr>
<tr>
<td>Gupta 1987 [31]</td>
<td>India</td>
<td>54</td>
<td>CLQ 300 mg, 1 or 2/wk</td>
<td>2 yrs</td>
<td>2 yrs</td>
<td>54 Improved</td>
</tr>
<tr>
<td>Mac Ounigbo 1992 [76]</td>
<td>Nigeria</td>
<td>39</td>
<td>PG 100 or 200 mg</td>
<td>2 - 12 mths</td>
<td>2 - 12 mths</td>
<td>All improved (10 cured)</td>
</tr>
<tr>
<td>Manenti 1994 [79]</td>
<td>Tanzania</td>
<td>312</td>
<td>PMT 25 mg/wk</td>
<td>1 mths</td>
<td>3 mths</td>
<td>208 improved 104 unchanged</td>
</tr>
<tr>
<td>A Elgayoum 2011 [18]</td>
<td>Sudan</td>
<td>54</td>
<td>Single short term treatment (various regimens)</td>
<td>1 d to 1 wk</td>
<td>15 -24 mths</td>
<td>36 improved 12 worsened 6 unchanged</td>
</tr>
<tr>
<td>Alkadarow, 2013 [69]</td>
<td>Sudan</td>
<td>33</td>
<td>CLQ 300 mg/wk</td>
<td>3 mths</td>
<td>3 mths</td>
<td>14/21 improved (12 lost)</td>
</tr>
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</table>

(CLQ = chloroquine; PG = proguanil; PQ = primaquine; PMT = pyrimethamine; NR = not reported)
Key messages from original *MMWR* article (Goers *et al.*, 2016)

- **Potential etiologies:**
  - 26.9% positive for malaria (RDT or thick smear)
  - 2.1% positive for *Schistosoma mansoni* ova (by stool)
  - 0.7% positive for previous *Leishmania* exposure (by serology)
  - 3.5% positive for HepBsAg.

- **Recommendations**
  - Pre-departure ACTs
  - Further laboratory and radiology testing after relocation
  - Empiric treatment with primaquine
**Ongoing Issues/Analysis**

--Many reports of cases not resolving, a few worsening
--Reports of complications (e.g. traumatic splenic rupture, surgical splenectomy)
--Non-falciparum malaria reports (particularly *P malarae*)
--Continued new cases, including from Tanzania
Investigation Timeline

Sept 2016: MMWR published on initial cases (Goers et al.)

Epi-Aid 2018-014 initiated

Allison et al. (2017)

Overseas Exam
March – July

U.S. Resettlement
June 2015 – Jan 2017

Clinician Reports
Oct 2016 – Present

Ongoing analytic projects

- **MMWR**
  - Follow-up to original MMWR, describe clinical characteristics and explore other potential etiologies:
    - Clinical progression associated with splenomegaly cases (and controls)
      - matched on age, sex, time of arrival, refugee camp, country of origin, and state of resettlement
Descriptive analysis

Clinical course of disease
Objectives

- Describe any diagnostic tests and alternative etiologies
- Characterize clinical progress
- Provide ongoing recommendations based on findings
Methods

- Engage state/local health departments, initial screening clinics, and refugee health providers
- Perform medical chart abstractions from initial screening, primary care, and referral care visits
- Calculate descriptive
Participating States

Original MMWR
• 145 cases, 23 states
Participating States

Original MMWR
• 145 cases, 23 states

Current Epi-Aid
• 93 cases, 9 states
Flow algorithm of patient inclusion in follow-up investigation

Pre-Departure Examination

- 145 overseas case-patients from original cohort, resettling in 23 states
- 42 case-patients identified outside of original cohort
  - 16 diagnosed overseas outside of original cohort, resettling to 6 states
  - 26 identified during post-arrival screenings in 6 states

Resettlement and Post-Arrival Exam

- 93 case-patients from original cohort, resettled in 9 participating states
- 135 case-patients

Domestic Medical Records Available

- 117 case-patients with available domestic medical records
  - 86 diagnosed overseas as part of original cohort
  - 10 diagnosed overseas outside of original cohort
  - 21 diagnosed after arrival

- 85 patients with splenomegaly after arrival
  - 64 patients with medical records ≥6 months after arrival
  - 21 patients lost to follow-up <6 months after arrival

- 35 patients with splenomegaly ≥6 months after arrival
Persistence

- 85 patients had splenomegaly at initial examination
- 64 patients had follow-up data beyond 6 months after arrival
- Median duration: 9.0 months (range: 0.3 – 27.9 months)
- 35 (54.7%) out of 64 patients had persistent splenomegaly
Familial clustering

- Ninety patients (66.7%) clustered in 22 families
- In New York State, clinicians identified six cases by proactively screening family members of known cases
  - Cases were detected by ultrasound, not by abdominal palpation
Treatment regimens

- All patients were treated with praziquantel (for schistosomiasis) and one dose of artemethur-lumefantrine before departure.
- Only 26.5% of patients received primaquine after arrival as recommended.
  - No one had documented completion of the 14-day regimen.
- Among patients who received primaquine, there was still some evidence of persistent splenomegaly.
Pre-departure malaria PCR studies

<table>
<thead>
<tr>
<th>PCR-positive</th>
<th>No. of positive specimens (n=144)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>83</td>
<td>58%</td>
</tr>
<tr>
<td>P. malariae</td>
<td>29</td>
<td>20%</td>
</tr>
<tr>
<td>P. ovale</td>
<td>12</td>
<td>8%</td>
</tr>
<tr>
<td>P. vivax</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>35</td>
<td>24% (21% for P fal/mal)</td>
</tr>
<tr>
<td>Any malaria detected</td>
<td>92</td>
<td>64%</td>
</tr>
</tbody>
</table>

Overall PCR in Hoima (different time)
--P.fal ~15% (vs 64%)
--P mal ~2% (vs 20%)
Limitations

- Irregular clinic visit intervals and loss to follow-up likely resulted in underestimates of splenomegaly duration
- Multiple data collectors across several states could have yielded some inconsistencies
- Standard of care (including diagnostic and prognostic tests) differs between clinics. This analysis used all available data.
Cohort study
Methods

- Controls of Congolese origin are matched to splenomegaly cases by:
  - Age (+/- 5 years)
  - Sex
  - Date of arrival (+/- 12 months)
  - State
  - Refugee camp
- Chart abstractions performed as before
- **Cohort** study because we knew that information on exposures would be inconsistent – easier to collect information on clinical manifestations to justify a subsequent case-control investigation.
Status

- Nearing completion of data collection
- Data collection has been completed in Arizona, California, Georgia, New York, Pennsylvania, South Carolina, Utah, and Washington
- Ongoing in Idaho, but should be complete in the next week or two
- Analyses are forthcoming
Future projects/questions

- Analyze cohort study (upon data collection completion)
- Case-control study to help identify etiology (perhaps in refugee settlement)?
- Epidemiology studies in refugee camps/settlements
Take-home points

- Come back from your happy place
Take-home points

- Splenomegaly etiology is still uncertain, malaria playing a role but it might be multi-factoral

- Persistence beyond 6 months was common, despite literature

- Health providers should proactively screen family members of known cases
Take-home points

▪ Health providers should provide primaquine after arrival (if G6PD levels are normal)

▪ Aware that there is break-through malaria

▪ Testing for other etiologies may be important (e.g. infections (schistosomiasis), non-infectious)
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It is time for parents to teach young people early on that in diversity there is beauty and there is strength

Maya Angelou

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