Introduction:

Welcome to CUGH's bi-weekly clinical case-series, "Reasoning without Resources," by Prof. Gerald Paccione of the Albert Einstein College of Medicine. These teaching cases are based on Prof. Paccione's decades of teaching experience on the medical wards of Kisoro District Hospital in Uganda. They are designed for those practicing in low resource settings, Medicine and Family Medicine residents, and senior medical students interested in clinical global health. Each case is presented in two parts. First comes a case vignette (presenting symptoms, history, basic lab and physical exam findings) along with 6-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. Two weeks later CUGH will post detailed instructors notes for the case along with a new case vignette. For a more detailed overview to this case-series and the teaching philosophy behind it, see Introduction to "Reasoning without Resources". Comments or question may be sent to Prof. Paccione at: gpaccion@montefiore.org

Note: If you would like to be notified when a new case is posted (along with instructor notes for the previous one), send your e-mail to Katherine Unger at kunger@CUGH.org.

About the Author:

Dr. Gerald Paccione is a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York. His career has centered on medical education for the past 35 years – as a residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and director of the Global Health Education Alliance at the school. He has served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. Dr. Paccione spends about 3 months a year in Uganda working on the Medicine wards of Kisoro District Hospital where he draws examples for the case studies.

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CASE 46 – Coughing Blood

A 19 year old woman from a remote village presents with six days of bloody sputum. She has been coughing for 5 months, mostly dry at first for months, then intermittently productive of white to yellow sputum. Three months ago, she found out she was pregnant with her second child, and shortly thereafter, that she was HIV positive on routine screening (no CD4 done).

Despite her pregnancy, she has lost 10kilograms, from 48 to 38 kgs. Six days ago she noticed blood in her sputum and over the past 5 days, *large amounts* of pure blood filling about a half to a full cup or more per day. She has not experienced this or any other lung problem before, and hasn't noticed fevers, hot/cold sensations, or night sweats. Neither shortness of breath nor chest pain accompanies the cough. There is no history of alcohol use, seizures or loss of consciousness; and no edema or leg pain.

Physical Exam:

Thin frail young woman, slight lower abdominal prominence; coughing blood during the interview and exam

B/P 110/60 without orthostatic changes; T 36; R 20; HR 96→100 sitting
HEENT: no jaundice; slight conjunctival pallor; PERRLA; Fundi, benign without exudates
Mouth: no thrush,
Neck: multiple "shoddy" nodes, < 1 cm diffusely, in cervical chain bilaterally; thyroid: palpable/normal;
Lungs: no crackles heard; possibly decreased breath sounds at left base; posterior left upper lung field 3-4cm area of loud clear hollow-sounding breath sounds "as if blowing across the top of a bottle"
Heart: PMI in 5th ICS; no LV heave or RV lift; S_1, S_2 without rubs or murmurs
Abdomen: no tenderness, masses or hepato-splenomegaly palpated
Extremities: no edema or pain;
Neurologic: intact; general muscle wasting but strength intact and symmetric

1. What is the "*frame*" in this case from the history and physical exam (i.e. the key clinical features the final diagnosis must be consistent with)?

- *HIV positive, pregnant*
- *chronic cough for months with gross hemoptysis*
- *weight loss*
- *focal breath sound abnormality*

2. What term has been used to describe the abnormal breath sounds in the posterior left upper lung field?

- *These have been called "amphoric" breath sounds – hollow and resonant, as if blowing across the top of a bottle. They sound like a more extreme version of tubular breath sounds, but in this case not air traversing a "tube" but rather echoing within an empty cavity.*
- *Amphoric sounds is a sign of a large cavity.*

3. What is the (near certain) diagnosis in this patient?
What are other possible diagnoses and why are they unlikely?

- *Cavitary tuberculosis is the near-certain diagnosis for many reasons: TB is endemic in Uganda; the patient is HIV (+), coughing for months, with weight loss. Invasive disease is likely with the bleeding, and there are no clinical suggestions of other causes of copious hemoptysis in a non-smoking, young woman. At least half of patients with active TB are not aware of a fever and don't have one on presentation.*
- *Other common causes of hemoptysis are all unlikely: pulmonary emboli (during pregnancy) doesn't explain the chronicity of symptoms, or the lack of dyspnea, edema, leg pain, or RV lift; bronchiectasis is unlikely without a prior history of copious sputum production, asthma, or prior pulmonary disease; bronchitis is inconsistent with the copious amount of blood, an etiology, the weight loss, or the duration of symptoms; rheumatic heart disease, especially mitral stenosis, isn't supported by the normal physical exam and absence of dyspnea; lung cancer is unlikely, despite its increased incidence in HIV disease, because of her youth and non-smoking status.*

4. What might be the mechanism of the hemoptysis in this patient?

- *Hemoptysis in TB, even if minor (and it usually is minor) is a late manifestation of disease caused by erosion of the inflammatory reaction into the bronchial wall or sloughing of caseous necrotic tissue into the airways.*

- *Massive hemoptysis is variably defined as 100-600 cc/24 hours, the lower range of which may be consistent with what this patient is producing. In TB, sudden massive hemoptysis is usually due to the rupture of a "Rasmussen aneurysm", a small-to-medium pulmonary artery branch, distorted by inflammation in the wall of a tuberculous cavity and/or transversing and suspended in it – which can cause exsanguination or asphyxia, and death.*

  Although something to consider, rupture of a Rasmussen aneurysm is not likely in this hemo-dynamically stable patient coughing blood for 6 days.

5. What is the immediate bedside therapeutic maneuver to be initiated in this patient?

- *As per conventional wisdom, lay the patient down and keep her on the side of the bleed. Lying on the side of the bleed prevents auto-aspiration, and tamponades the bleeding vessel(s).*

  Luckily the amphoric breath sounds indicate the likely source of the blood in this patient, but often it's not as obvious. Sometimes with bilateral disease localization is difficult, and if blood spills into the other (normal) lungs, crackles can be misleading (as well as "infiltrates" on CXR).
  N.B. The caveat here is that most people with cavitary TB and/or a long history of symptoms prior to presentation do have extensive disease on X-ray (and even more on CT). The most obvious exam abnormality may not be the source of the bleed.

6. What does the PE suggest about the patient's CD_4 count?

- *Both the presence of a cavity and the upper lung field localization suggest a relatively preserved inflammatory response and immune function. Lower lung field and miliary disease ("atypical" pulmonary presentations) become more common as the CD_4 count drops.*

7. **What are the therapeutic challenges in caring for this patient?**

- *Cavitary disease implies a huge mycobacterial burden, averaging $>10^{9\text{-}12}$ organisms because cavities are a luxurious growth medium for TB bacilli. (TB with infiltrate alone has an average of $10^{6\text{-}8}$ organisms).*

- *Mycobacterial burden influences drug strategy and was the reason, in the pre-INH, pre-MDR (multi-drug resistance) era, that "cavitary TB" was an indication for 3 drugs vs. (the usual, at that time) 2 drugs.*

  A mutation to an anti-TB drug occurs ~ 1 in 10^6 organisms (10^6 for INH, 10^8 for rifampin); and to 2 drugs simultaneously in about 1 in 10^{12}. Thus if infiltrates have (only) 10^{7-8} organisms, treating with 2 drugs carries only a 1/10,000 risk or less of a resistant organism emerging naturally; likewise if cavities have 10^{12} organisms, 3 drugs should cover it well - 10^{18} organisms before a mutation would appear. With TB, such over-kill is important.

- *The current reason for the 4 drug initial therapy guidelines for all TB has to do with the emergence and spread of MDR TB, and to facilitate short-course therapy. You don't want to miss just in case the TB is resistant to one antibiotic already!*

- *4 drug therapy uses pyrazinamide (PZA): PZA is "unknown" vis-a-vis safety for the fetus. Thus we are either left with INH, rifampin, and ethambutol…for cavitary disease, or risk PZA therapy. PZA has been a very important enabler of short course therapy for TB, and given the severity of disease in this patient (TB is itself very detrimental to the fetus) and the "unknown" fetal safety of the drug, it is probably wise to treat the mother with all 4 drugs. Streptomycin, a potential replacement for PZA otherwise, is contraindicated in pregnancy.*

- *The other major management questions are whether and when to start HAART therapy for co-existing HIV. Evidence is strong that in patients with CD4 counts below 200, starting HAART during TB treatment significantly decreases mortality - despite the challenges of adherence to a number of new drugs for 2 new (devastating) diagnoses, and the CAMELIA trial demonstrated a 34% mortality decrease for patients started at 2 weeks vs. 8 weeks of therapy. (Recent evidence suggests that HAART therapy should be started in patients with active TB independent of the CD4 count.) Efavirenz is the NNRTI of choice in patients being treated for TB.*

  Thus optimal therapy in this patient, after documentation of TB by smear, includes starting HAART within a few weeks of starting TB medications.

Suggested Reading:

Friedan T Tuberculosis Lancet 2003; 362: 887–99

Maartens G, Wilkinson RJ Tuberculosis Lancet 2007; 370: 2030–43

Lee JH, et al., Haemoptysis due to chronic tuberculosis vs. bronchiectasis: comparison of long-term outcome of arterial embolization INT J TUBERC LUNG DIS 2007 11(7):781–787

Sterling TR et al., HIV Infection–Related Tuberculosis: Clinical Manifestations and Treatment CID 2010:50 (Suppl 3) • S223

Gadkowski BL, Stout JE Cavitary Pulmonary Disease CLINICAL MICROBIOLOGY REVIEWS, Apr. 2008, p. 305–333

H. Simon Schaaf, A Zumla; Tuberculosis: A Comprehensive Clinical Reference 2009, Saunders
Shapira JD. The Art and Science of Bedside Diagnosis. Baltimore, MD: Urban & Schwarzenberg; 1990