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 Jillian Morgan at jmorgan@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 23 – COUGH PLUS

A 45 year old male, a farmer who lives with his wife and 4 of their 10 children, is referred by the Village Health Worker after a routine home visit.

He complains of increasing fatigue over the past month and 10 days of cough. He felt well until about a month ago when unusual fatigue began while digging in his field. Ten days ago (in Church on Sunday) he began to cough; the cough is mostly "dry", but recently has been intermittently productive of white-yellow sputum. Always thin, he's not sure if he lost any weight, "maybe a kilogram". He's had no shortness of breath or night sweats, and although he denies fever, he says he's felt "hot" on and off.

Over the past 6 months he's been increasingly bothered by a diffuse skin rash, particularly over his arms and legs but also on his chest and back, that itches a lot. In the past, he worked seasonally in Kampala, but not for the past 10 years.

P. E. Sitting in bed on the ward, in no distress

BP 105/75 HR 95 RR 20 T 100.5 axillary

Skin: firm, discrete .3-1cm, erythematous, urticarial papules

diffusely, with excoriation, arms/legs > chest/back; otherwise normal;

nails without fungal infection

HEENT: normal; mouth: no thrush

Eyes: sclera white; fundi, benign without papilledema, exudates;

Neck: thyroid normal, LAD: 1-2 cm diffuse, mobile, non-tender;

lungs clear, with occasional "squeak"/wheezing right base; no dullness

heart: S1, S2 split physiologically;

abdomen: no masses, no hepato-splenomegaly; non-tender

neurologic: mental status, cranial nerves, sensory/motor/cerebellum/gait normal

1. **What is the "frame" of this case (i.e. the key clinical features the final diagnosis must be consistent with)?**
   What is the clinical relevance of the items selected?

   - *45 year old man, who used to do migrant work (Migrant work increases the chances that HIV was acquired sexually, during peak years of the HIV epidemic in Uganda)*
   - *6 months of pruritic skin rash (suggests that an underlying chronic inflammatory disease, like HIV, may be present)*
   - *1 month of unusual fatigue, and 10 days of progressive cough, in no distress (The fatigue, indolent nature of the cough, and lack of acute distress suggests a chronic process, specifically not an aggressive pyogenic bacterial pneumonia)*
   - *Denies fever, not conscious of the fever he has (suggests an indolent inflammatory process)*
   - *Referred by the VHW, not sick enough to feel he needs hospitalization. (The "iatrotropic stimulus", the reason people come to medical attention, is an important predictor of the type of underlying problem present. In this case it corroborates the indolent nature of the disease, as do other observations above.)*

2. **What are the clinical implications of the following PE findings: temperature, skin lesions, lymphadenopathy, lung exam?**

   - Temperature 100.5 axillary, *(probably >101 rectal, a "fever", as axillary temperature is normally 1-2 degrees F below rectal/core temperature)*

   - Skin: firm, discrete .3-1cm, erythematous, urticarial papules diffusely arms/legs > chest/back; *(suggests "papular prurigo", an HIV-associated dermatosis probably secondary to a hypersensitivity reaction to insect bites)*

   - LAD, diffuse, 1-2 cm *(consistent with underlying HIV; likely not disseminated TB in this patient, without weight loss/cachexia)*

- Lung: clear, with occasional "squeak"/wheezing right base; no dullness *(focality on exam suggests pulmonary focus of pathology, and not diffuse as in bronchitis; no crackles/dullness make it less likely to be a consolidating pneumonia than a process distorting/partially obstructing the airway.)*

3. What are some history/physical exam clues to the presence of underlying chronic disease in Africa that the clinician should look for?

- *Superficial fungal infections related to HIV: oral thrush; chronic/recurrent candidal vaginitis; chronic nail infections due to candida (early) or T. rubrum (CD4<100, often affecting all nails);*
- *Lymphadenopathy, diffuse, mobile, small 1-2 cm;*
- *Dermatologic clues to HIV:*
  - *Herpes zoster scar*
  - *Papular prurigo*
  - *Seborrheic dermatitis*
  - *Oral hairy leukoplakia*
  - *Molluscum contagiosum*
  - *Oral or dermal Kaposi Sarcoma (purple macules/papules)*
- *Chronic constitutional symptoms: fevers, weight loss*
- *Chronic diarrhea*

4. What are the "duration of illness" guidelines when evaluating "cough" in African hospitals?
How can the clinician use "severity of illness" as a diagnostic clue?

- *Bacterial community-acquired pneumonia (CAP) usually evolves rapidly: in the U.S. patients usually come to medical attention within 2-3 days. Although in Africa patients often wait longer to come to the hospital/clinic, fewer than 5-7 days of symptoms suggests a pyogenic process.*

- *Symptomatic TB, a more indolent process, usually presents after weeks of symptoms. Symptoms for more than 2 weeks are highly suspicious for TB.*

- *In the hospital setting, duration of symptoms combined with severity/acuity of illness are valuable clues: in pyogenic bacterial pneumonias patients "look sick" (increased fever, respiratory rate, SOB, or lethargy, etc.) with an illness of days duration. Most of those with symptomatic TB don't look acutely ill unless the disease is late stage and/or a bacterial pneumonia is superimposed*

(and the course of disease progression has changed within days). Significant focal lung findings (e.g. crackles/dullness over >25% of a lung field) in patients who are not acutely ill, is highly suspicious for TB.

5. Why is inquiry about "cough" commonly used for screening in many communities and ambulatory care settings in Africa?
How accurate are clinical features in diagnosing the cause of cough in these settings?

- *Interest in screening for TB in Africa stems from desire to*
  a) treat patients earlier in their course of disease, a major factor in survival;

  b) limit transmission to others;

  c) treat HIV+ patients with ART while mitigating IRIS reactions in co-infected patients with active, untreated TB;

  d) prophylax high-risk patients with HIV with INH - which risks selecting for INH-resistance if TB is active and a multi-drug regimen is not used.

- *The accuracy of symptoms in predicting positive TB cultures heavily depends on the study setting: in hospital or clinical settings where patients are symptomatic, most patients diagnosed with TB have had symptoms for >2 weeks and the sensitivity of chronic cough is high (>90%). On the other hand, screening for TB in HIV clinics before starting ART or INH prophylaxis, or routine screening in populations with high-TB prevalence, reveals that 25-65% of those with TB-positive sputum cultures either have no cough or cough for <2 weeks.*

- *In screening HIV+ patients in SE Asia, the presence of a cough for 2 or 3 weeks or more during the preceding 4 weeks had a sensitivity of (only) 22 to 33% for detecting tuberculosis. The sensitivities of isolated symptoms in the past 4 weeks - e.g. of <u>any</u> cough, fever, weight loss, or fatigue - were each only ~ 70%. However, in combination, the presence of <u>cough of any duration</u>, <u>fever of any duration</u>, or <u>night sweats lasting 3 or more weeks in the preceding 4 weeks</u> was 93% sensitive and 36% specific for tuberculosis. This means that 93% of patients with TB had at least one of these findings, but that 64% of patients without TB also had one (90% of these TB cases were smear (-), culture positive). (NEJM 2010; 362:707-716)*

- *In a study in Uganda where HIV patients with TB had more advanced disease, a TB screening study among HIV+ patients found a sensitivity of 99%, specificity 66%, and NPV of 100% if any of the following were positive: cough > 3weeks (seen in ~50% with TB), fever > 4weeks, lymphadenopathy, BMI<18. This means that if the patients in this study had none of these findings, they did not have TB (Int J Tuberc Lung Dis 13(4):508–513).*

- *In HIV+ patients, cough for >2 weeks is commonly found in conditions other than TB (PPV ~25%). In population screening in an inner city slum in Kampala (high TB prevalence), 18% with cough >2 weeks had TB. Thus, in screening settings, 70-80% of patients coughing for >2 weeks have something else causing it.*

6. What is the most likely diagnosis in this patient?
What is the differential diagnosis?

Indicate the clinical "pros and cons" for each of your choices.

- *Tuberculosis is the most likely diagnosis in this patient: TB is suggested by the chronicity of the fatigue (1 month) with cough of more than a week, the focal lung finding even in the absence of crackles (peri-bronchial reactive nodes can narrow airways causing wheeze), the fever of which the patient is unaware (suggesting an indolent process), and the exam clues suggesting underlying HIV. N.B. Although chronicity of cough is more predictive of TB in HIV(-) patients, that's because there are more non-TB possibilities that cause chronic cough in HIV+ patients.*
- *Asthma, "subclinical", causing cough, with only a trace of a wheeze in one area. Allergic asthma is sometimes induced by HIV's effect on the helper-suppressor T-cell balance and immune system function. However fever is not seen in asthma alone, and would suggest an infectious precipitant to the bronchospastic episode.*
- *Bronchitis, viral or bacterial, could produce cough of 10 days duration. However in this patient, the absence of diffuse rhonchi in a process entrenched enough to elicit a fever makes this possibility far less likely.*
- *HIV-related fever and fatigue, with another cause of cough (viral respiratory illness). In Africa, limited access to care, poverty/malnutrition and HIV all make dual diagnoses more common.*
- *Mycoplasma bronchitis/pneumonia. Mycoplasma infection is sub-acute, presents to medical attention after an average of 2 weeks of symptoms, and often has few lung findings. It's not HIV-related, but is common.*

- *PCP: a cause of sub-acute cough and fever in late-stage HIV, the absence of dyspnea makes PCP unlikely, as does the sputum our patient is producing.*

7. What 2 tests would you order initially?

- *AFB smear*
- *HIV test*

8. What are the implications of (possible) HIV on diagnosis and treatment of the presenting disease in our patient?

HIV immune suppression is the root cause of the resurgence of TB worldwide, one of the major opportunistic infections (OI) in AIDS, and the leading OI and most common cause of AID-related death in Africa. Over 70% of new cases of TB in Africa are HIV-associated, and although the risk of TB increases with increasing immune suppression, TB is a virulent organism frequently causing disease in people with CD4 counts above 350-500.

HIV influences the presentation of TB:

- *The constitutional symptoms of the two diseases overlap and HIV is associated with other OIs that can mimic TB: thus chronic cough is less specific for TB in HIV patients, more symptomatic patients with HIV+/TB than HIV-/TB have weight loss (>50%) and drenching night sweats (~50%);*
- *There's more asymptomatic or minimally-symptomatic sputum-culture (+) TB in HIV patients;*
- *Extrapulmonary TB is seen in 40-80% of HIV+/TB vs. 10-20% HIV-/TB.*

HIV influences the diagnosis of pulmonary TB:

- *Sputum smear: in clinical settings, ~50% of HIV/TB is smear (-) (2-3 smears)*

- *Culture: in screening studies, solid phase cultures can be false negative in 30-40% (gold standard being combination of symptom and x-ray response to therapy);*
- *X-ray: radiographic appearance is atypical with depressed CD4 counts: Cavitary TB is infrequent, lower lobe TB common, and normal x-rays are seen in up to 20% with active pulmonary TB (culture +).*

HIV influences TB treatment:

- *Absorption of rifampin and PZA is often decreased in HIV patients, and INH peak drug levels are lower in patients with HIV diarrhea; low levels can be a cause of TB treatment failure; (Ann Intern Med. 1997;127:289)*
- *Rifampin increases metabolism of many ART drugs, requiring change to rifabutin (more expensive, less available).*

9. What should you do if the HIV test is positive but your diagnostic test-of-choice for the presenting illness is negative?

- *As a generalization, <u>symptomatic</u> HIV+/TB patients are more likely than non-HIV TB patients to be smear ⊖ … nearly 50% (N.B. smear (-) means <10,000 AFB/ml sputum). In screening studies in <u>asymptomatic</u> persons i.e. in whom symptoms haven't yet caused them to seek care, 60->80% of those with TB (culture positive) are smear negative.*
  Our patient, referred by a VHW making home visits, fits between these two settings, probably closer to the screening situation since the VHW was "case-finding", symptoms were of short duration (fatigue for a month and coughing 10 days), and the exam had minimal findings. So we shouldn't be surprised by a negative smear, even if the patient has TB.

- *Although no longer recommended, in resource poor settings the next step <u>used to be</u> to first use empiric therapy against pyogenic bacteria as a diagnostic test before treating suspected TB: i.e. give a trial of ampicillin or amoxicillin for community-acquired pneumonia or bronchitis - while following fever, subjective response, exam, and cough. If no improvement was apparent in 5 days, another round of a different antibiotic was suggested by some authorities and guidelines, this time erythromycin for the "atypicals" Mycoplasma or Chlamydia (avoiding a quinolone since quinolones cover TB too). And at that point, if available, a CXR for an infiltrate was recommended.*
  If the patient responded symptomatically and there was an infiltrate on x-ray, treatment for TB would be withheld and a follow-up CXR would be done in 2-3

weeks to make sure the "improvement" wasn't from a placebo response by a patient wanting to go home.

If the patient didn't respond to therapy with antibiotics, empiric TB therapy would commence.

Even if a patient with suspected TB responded to antibiotics, close follow-up was all-important in this empiric strategy because misinterpretations of empiric-therapy-as-diagnosis were frequent: Besides being thrown off by a placebo response to antibiotics, clinicians suspecting TB in HIV+ patients are also frequently dealing with 2 pathogens – chronic TB and an acute pneumonia – and can be tricked by the transient response to antibiotics for the superimposed bacterial infection. After many more weeks or months of spreading disease and getting sicker, these patients re-present with full-blown TB. As important as close follow-up was to the strategy of initial empiric antibiotic therapy, it wasn't supported by directly-observed therapy (DOT) – as would accompany a TB diagnosis - to ensure/improve adherence with follow-up.

Thus, in the latest WHO guidelines for suspected smear (-) TB in HIV (+) patients, empiric antibiotic therapy against pyogenic organisms is NOT recommended: responses are too often misinterpreted by patients and clinicians, the risk of harboring TB is greater in HIV (+) patients, the smear is more likely to be falsely negative, and the disease is more likely to progress quickly and be fatal. X-ray and simply empiric therapy against TB is recommended.

The empiric antibiotic strategy can be used in HIV (-) patients with suspected TB.

- *Strongly consider treating for TB in HIV (+) patients even without an infiltrate on CXR, since as many as 20% with HIV+/pulmonary TB may not have an infiltrate.*

- *Full-dose empiric therapy for TB should be continued at least 1-2 months while the patient is closely monitored for response. If a response is seen, finish the full course.*

Suggested Readings:

Barnes, P.F., et.al; The course of fever during treatment of pulmonary tuberculosis Tubercle (1987) 68: 255-260

Resneck, J.S., et.al; Etiology of Pruritic Papular Eruption With HIV Infection in Uganda JAMA. 2004;292:2614-2621

Corbett, E.L., et.al; Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment *Lancet* 2006; 367: 926–37

Lockman, S., et. al; Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana INT J TUBERC LUNG DIS 2003 7(8):714–723

Getahun, H., et.al; Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes *Lancet* 2007; 369: 2042–49

Reid, M.J.A., Shah, N.S.; Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings *Lancet Infect Dis* 2009; 9: 173–84

Kahn, M.S., et.al; Improvement of tuberculosis case detection and reduction of discrepancies between men and women by simple sputum-submission instructions: a pragmatic randomized controlled trial *Lancet* 2007; 369: 1955–60

W. Were, et.al; A simple screening tool for active tuberculosis in HIV-infected adults receiving antiretroviral treatment in Uganda INT J TUBERC LUNG DIS 13(1):47–53

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

Chamie, G, et.al; Tuberculosis as Part of the Natural History of HIV Infection in Developing Countries CID 2010:50 (Suppl 3) • S245

Karim, S.S.A.et.al; Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy N Engl J Med 2010;362:697-706.