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 32 – Wasted from Kampala

A 23 year old woman is brought to Kisoro District Hospital after a 10 hour bus ride from Kampala. HIV was recently diagnosed 2 weeks ago after a wasting illness of more than 6 months and she was then abandoned by her husband with whom she had gone to Kampala about 3 years ago. She is now returning to her family. Her CD_4 count was found to be 27 in Kampala prior to her return to Kisoro, and treatment was neither given nor planned as she recalled.

She complains of dry cough for over 2 months without sputum, slowly growing lumps in her neck for months, vomiting with decreased oral intake for weeks, and diarrhea (watery, without blood, about 4-6x/day) for 1week. She's had no abdominal pain, headaches, or fevers that she's noted. She's been too weak to walk for 3 days and is being carried in by her family.

Physical Exam:

Very cachectic, weak, but fashionably dressed and fully made-up, tearing and distraught

BP 64/40 (repeated x2); HR 80; T^o 92^o per rectum R 24

mouth: thrush diffusely; no violaceous macules/plaques on palate

eyes: no icterus;

fundi: discs sharp; right eye 2 round white opacities ~ .1-.2 disc diameters in size, at 11:00/6:00, 1 and 3 disc diameters away

neck: supple to movement in all directions

firm, non-tender, non-fixed 1-2cm lymph nodes in posterior cervical chain bilaterally

thyroid normal;

lungs: dullness to percussion bilaterally at the bases, with overlying *increased* breath sounds without crackles but prolonged expiratory phase;

cardiac: S_1 S_2 without murmurs, rubs

abdomen: liver span ~ 12cm to percussion, 3cm below costal margin, non-tender;

spleen tip palpable, decreases 2 cm on inspiration

no distention, masses, guarding or tenderness

no edema, skin rash or nodules

N.B. X-rays were unavailable during this patients admission (machine "down" for a month)

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

- ***HIV ⊕ with thrush and severe wasting***
- ***hypotensive, hypothermic***
- ***cough (dry) >2 mos***
- ***cervical LAD, hepato-splenomegaly***
- ***fundal opacities***

2. Can this be simply a presentation of end-stage AIDS, "slim disease"? Explain.

- *Many features are consistent with end-stage HIV and wasting including lymphadenopathy (LAD), diarrhea, hypotension.*
  However, cough, ocular opacities and the size and recent development of the lymphadenopathy suggest that an underlying chronic opportunistic infection is causing her relentless deterioration.

3. What are the key findings on Physical Exam and the clinical significance of each?

- *hypotension: the relevant differential diagnosis includes: decreased intake with diarrhea/vomiting, sepsis, chronic wasting, adrenal insufficiency*

- *hypothermia: suggests sepsis or adrenal insufficiency*

- *HR only 80: hypothermia can cause bradycardia*

- *Lymphadenopathy, spleen palpable 2 cm below costal margin, probable hepatomegaly: implies diffuse reticulo-endothelial involvement, although the 3 findings can have independent etiologies especially in Africa and in patients with AIDS;*

- *lungs: no crackles but increased breath sounds and dullness – a lung exam without crackles is found in hematogenous dissemination of TB (i.e. miliary); the increased breath sounds and dullness could be due to late coalescence of growing miliary nodules (plus severe asthenia) or consolidated lung which became the focus of later miliary spread. N.B. Cough is seen in (only) ~ 1/3 of patients with miliary TBC.*

- *eyes: fundi reveal (probable) "choroid tubercles", seen in 20% with miliary TB*

4. Diagnosis in this case involves identifying both the clinical *syndromes* the patient presents with and the underlying *etiologies* responsible for both her chronic illness and acute deterioration.

a) Identify the relevant clinical syndromes in this patient's presentation.

b) What etiologies should be considered? What is the most likely, and why?

- *There are at least 2* ***syndromes*** *(i.e. constellations of clinical abnormalities linked by common pathophysiology) evident on initial presentation: one acute, characterized by hypotension, hypothermia, and diarrhea; and one chronic, characterized by chronic cough, wasting, and diffuse reticulo-endothelial activation.*

- ***Acute: hypothermia/hypotension/diarrhea****:*

This combination of findings suggests ***sepsis, adrenal insufficiency,*** *or* ***both.***

Sepsis *releases cytokines that stimulate the GI tract inducing diarrhea and vomiting, and others that cause hypothermia. The hypotension can be a sign of resulting volume depletion, or septic shock.*

Adrenal insufficiency (Addison's disease) with adrenal crisis *also causes hypothermia, hypotension, and diarrhea/vomiting.*

- Chronic: cough, wasting, and diffuse reticulo-endothelial system (RES) activation (lymphadenopathy, hepato-splenomegaly)

This combination of symptoms and exam findings suggests a diffuse chronic infection within the lung and RES, with probably a granulomatous inflammatory response in multiple organs.

A reticulo-endothelial neoplasm, such as a virally-induced (EBV) lymphoma or Kaposi's sarcoma (KS, HSV 8) in this AIDS patient is also plausible, but there are no other skin or oral manifestations of KS, and the RES involvement is less impressive than one might expect for a neoplasm like lymphoma that would be otherwise pre-terminal.

- *The specific infectious* ***<u>etiologies</u>*** *(of these syndromes) that should be considered include:*

- Acute: hypothermia/hypotension/diarrhea*:*

<u>If sepsis-induced</u>: In late-stage AIDS patients in Africa pneumococcus, non-typhi salmonella (NTS), and mycobacteria (TB) are the most prevalent causes of bacteremia. All can cause the "sepsis syndrome", including diarrhea.

<u>If adrenal insufficiency-induced</u>, disseminated TB, the major cause of Addison's in Africa, is the likely culprit, perhaps abetted by HIV involvement of the adrenals. In this late-stage AIDS patient, hypoadrenalism can be complicated by bacterial sepsis inducing an overt Addisonian crisis.

- Chronic: cough, wasting, and diffuse reticulo-endothelial system (RES) activation

The most likely cause of the patient's chronic deterioration is ***disseminated TB*** *involving lung, spleen, liver, lymph nodes, and choroid. Other infectious possibilities include disseminated Cryptococcus which can involve meninges, liver-spleen-nodes, skin, and lung (pulmonary involvement in ~20%); chronic salmonella infections, NTS or S. typhi, and another mycobacterial disease, MAI.*

TB is the most likely because TB is the most common opportunistic infection in HIV (+) patients in Africa, its incidence rises markedly with progressive immunosuppression, and it classically involves and induces granulomas in the many organ systems affected in this patient. TB is far more common than MAI in Africa (although not in the West).

Furthermore, TB is more consistent with the patient's long duration of illness than is salmonella sepsis, better fits the overall (probability) distribution of positive and negative findings than Cryptococcus or salmonella, specifically causes the ocular findings noted on exam, and can explain all features of both the chronic and acute syndromes being considered in this patient.

- *"Disseminated TB" implies active disease in 2 or more non-contiguous organs, while "miliary TB" is disseminated TB that appears on chest X-ray or CT scan as 1-2 mm nodules diffusely scattered throughout the lungs, implying hematogenous dissemination. Most disseminated TB is blood-borne, and the two terms are often used synonymously (although for linguistic purists, disseminated TB with a clear chest x-ray is not "miliary" per se). In this case, without an x-ray available, "disseminated" is most appropriate. However, the choroid tubercules seen in this patient are ocular analogs of the millet seed-size shadows in the lungs, and probably meet the formal definition of "miliary TB".*

5. Which organs are most frequently involved in this disease process, and what are its most common presenting symptoms?

- *Disseminated/miliary TB most frequently involves the lungs (with miliary shadowing on CXR appearing only after 3 weeks of illness in most cases), lymph nodes, liver, spleen, bone marrow, meninges, bones, kidneys, adrenals (most often asymptomatically).*

- *Symptoms are primarily constitutional: malaise/weight loss and fever/night sweats – each seen in ~70-90% of patients. Organ-specific manifestations are less common: cough in 30-40%; headache (from associated meningitis), 20-30%; lymph node enlargement ~20%; hepato-splenogmegaly, up to 20%; choroid tubercles, up to 20%.*

- *A "cryptic" form of miliary TB has been described in geriatric patients with constitutional symptoms and intermittent fever, possibly pancytopenia or leukemoid reaction, and only rarely a miliary pattern on x-ray, lymphadenopathy, or meningitis.*

6. What available diagnostic tests might confirm the diagnosis?

- *Chest x-ray evidence of classic "miliary" TB is present in ~50% (<u>only</u>) of patients: miliary lesions are <2mm (up to 3mm in 10%), widely distributed and roughly uniform in size; non-miliary patterns are seen in 10-30% - coalescence of nodules, mottled, "snowstorm", or ARDS.*
  Many other findings are associated with miliary TB: intrathoracic LAD, pleural effusions, pulmonary infiltrates/cavitation, pneumothorax, etc. Some x-rays are clear: it takes at least 2-3 weeks of hematogenous seeding (and symptoms) to produce the miliary pattern on chest x-ray.

- *Sputum should be checked for AFB, but will rarely be positive in this hematogenously-disseminated disease that involves primarily the pulmonary interstitium, not the alveoli. The source of the dissemination could be an active pulmonary lesion which produces a positive AFB smear.*
- *N.B. Urinalysis is often (non-specifically) abnormal, a sign of renal involvement: proteinuria, pyuria, and hematuria are all consistent with the diagnosis of miliary TB.*

  <u>N.B. During this patient's admission, the CXR was "down" and no x-rays could be taken.</u>

7. In this case, which 3 *diagnostic* questions could an empiric *treatment* strategy help address?

Describe a treatment approach for this patient that answers key diagnostic questions.

- *3 Diagnostic questions that empiric therapy can address:*
  a) Is the hypotension due to hypovolemia or to septic shock/hypoadrenalism?

  b) Is Addison's likely?

  c) Is non-mycobacterial sepsis likely?

- *<u>Is the hypotension due to hypovolemia or to septic shock/hypoadrenalism</u>?*
  This is best addressed by administration of IV fluid, rapidly - a "fluid challenge":

  When used as a diagnostic test for hypovolemic shock, saline must be given quickly as a measured IV bolus so all the fluid stays in the plasma space for the diagnostic assessment - measuring the acute response of BP and HR. If infused at the usual therapeutic repletion rates of 100-300 cc/hour, equilibration with the larger interstitial space may take place decreasing its effect on the BP/HR and possibly leading to a (false) negative interpretation of the test challenge – delaying diagnosis and appropriate management.

- *<u>Is Addison's likely</u>?*
  There are no cortisol levels to measure in African district hospitals, so a diagnosis of hypo-adrenalism depends largely on clinical observation and the response to empiric therapy with steroids.

  Three clinical observations are important: blood pressure, urine concentrating ability, and urinary response to fluid and steroids.

  - blood pressure: in the case of Addisonian crisis, IV steroids lead to an immediate, unambiguous increase in blood pressure.

  - urinary concentrating ability and response to fluids: due to renal tubular dependence on cortisol, the urine, even from a volume depleted patient, can't be concentrated and

the patient is unable to retain the fluid administered intravenously: the blood pressure will not respond, the fluid will be excreted, and the patient will become polyuric - even while in shock and volume depleted. Steroids reverse that.

- *<u>Is non-mycobacterial sepsis likely</u>?*
  This question can be (partially) addressed by the response to antibiotic withdrawal after the patient stabilizes. See below. Most of the time, this strategy is unnecessary since treatment for bacterial sepsis is short-lived. Why not just finish the course? However, when an alternative diagnosis such as TB is more likely and its treatment far more prolonged and complicated, getting the specific diagnosis may be important.

In this patient:

1) 500cc NS over 15 min led to a systolic BP increase of 15mm, to 75mm, and within 30 minutes, the beginning of urine output (a catheter was passed temporarily for acute monitoring). The BP stayed at ~75mm after 2 liters were administered within the first hour, while the urine output, initially sluggish and with *high* specific gravity, gradually increased and became less concentrated.

The response to the IV fluid "challenge", assessed by both the change in BP and urine output, strongly suggested volume depletion as the cause of the hypotension. (N.B. Blood pressure in rural Africa tends to run low, more so in malnourished, cachectic patients. The expected systolic BP of a patient like this one would be expected to be 75-90 at baseline.)

2) Since in this patient the initial urine was concentrated, the BP did respond to fluid by >10 mm, and polyuria was not seen with fluid administration, Addison's was thought to be unlikely. Nevertheless, since the stakes were high, empiric therapy was tried: After 2 liters, 50mg hydrocortisone was given IV – there was no change in BP, urine output, or patient well-being noted.

Thus, Addison's was clinically ruled out.

3) Although in this patient the positive response of both the BP and urine output to the initial fluid challenge supported the diagnosis of hypovolemia over sepsis as the etiology of the patient's hypotension, it did not rule out a serious bacterial infection in this extremely ill patient. Malnutrition, TB, and HIV predispose to bacterial infections, and in debilitated hosts a complicating bacterial infection "can't be missed".

So, despite the lead diagnosis of miliary TB (which could explain everything) the patient was initially treated for both TB and bacterial sepsis, covering non-salmonella typhi and pneumococcus, the two most common (non-TB) causes of bacteremia in HIV patients in Africa.

She felt "better" after 2 days, vomiting and diarrhea decreased, and appetite improved.

Once over the high-risk mortality period of 3 days, antibiotics against non-mycobacterial sepsis were discontinued and only TB treatment continued. The patient was closely observed: any symptomatic relapse would have triggered resumption of antibiotics. Most of the time, this strategy is unnecessary since treatment of bacterial sepsis is short-lived. Why not just finish the course? However, treating multiple possibilities, although essential on admission, would have muddied the water of diagnosis. When an alternative like TB is more likely and its treatment far more prolonged, complicated and possibly toxic than an alternative like bacterial sepsis, diagnostic assurance is more important.

Her cough decreased, she continued to feel better, began to walk again and gained weight – on TB treatment only. (No sputum was ever produced).

Plans were made to begin HAART therapy as an outpatient after adherence was assured.

Suggested Readings:

H. Simon Schaaf, A Zumla; Tuberculosis: A Comprehensive Clinical Reference 2009, Saunders

Sharma S.K, et.al.Miliary tuberculosis: new insights into an old disease Lancet Infect Dis 2005; 5: 415–30

Tanoue, L.T., Mark, E. Case 1-2003: 43-Year-Old Man with Fever and Night Sweats NEJM 2003; 348: 151