Introduction:

Welcome to CUGH's monthly 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 Eleazar Gutierrez at egutierrez@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 56- What Now ii

A 23 year old woman, recently homeless and abandoned by her husband, was diagnosed with HIV (CD_4 15) and miliary TB a month ago. She now presents to the hospital 4 weeks post-discharge with increasing headaches and confusion, and a seizure on the morning of admission.

The patient had had a long wasting illness before presenting to KDH with over 2 months of dry cough, severe cachexia, inability to walk, diffuse LAD, clear lungs with no sputum production, and mild hepato-splenomegaly. She had no fever or headaches. Disseminated TB was diagnosed empirically and she responded to TB therapy with increased strength, weight gain and decreased cough, and she was sent home after 2 weeks in-hospital to be cared for by relatives, with directly-observed therapy for TB and SMX-TMP prophylaxis. Plans were made to start anti-retroviral drugs (ARVs) for HIV after 1-2 months of TB treatment when follow-up and adherence were assured.

She did well at home for an additional 2 weeks, adherent to TB DOT and SMX-TMP therapy according to the family who administered her medications. During the third week she began to complain of increasing headaches which woke her from sleep, and after 7 days of headaches appeared intermittently confused to family members. On the morning of admission she fell to the floor unconscious, and began shaking all extremities uncontrollably and foaming at the mouth. Neither fever nor cough were noted.

Physical Exam: Carried to a bed by family members, dazed, confused, lethargic
BP 130/85; HR 60 and reg R 15 T 36
eyes: full ROM, PERRLA
fundi: white opacities (unchanged) in right eye; ? blurred discs bilaterally (difficult exam)
no thrush: tongue – swollen, lacerated, oozing blood
neck supple; posterior cervical LAD 2-3cm, increased from 1 month ago (prior to therapy)
lungs: clear; heart: normal PMI; normal S_1, S_2
abd: mild hepato-splenomegaly, unchanged, non-tender
neuro: lethargic; Cranial Nerves grossly intact;
motor: left pronator drift (repeated x 3); ? LUE 4/5; otherwise 5-/5
sensory, cerebellar, gait: unable to assess

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)?

- *recent diagnosis and treatment of miliary TB 1 month ago, with response initially*
- *headache, confusion, seizure evolving over 1 week: progressively worsening*
- *HIV ⊕ with CD_4 15*
- *adherent to therapy: TB and SMX-TMP*
- *no ARV's started*
- *PE: papilledema (?), left arm focality; lymphadenopathy increasing*

2. What are the WHO (and CDC) guidelines for starting ARV therapy in newly diagnosed patients with HIV and TB?

WHO guidelines:

- *if CD_4 <200, or extrapulmonary disease, start ARVs within 2 months of TB Rx*

- *if CD_4 < 50, start within 2 weeks*

Salim, et al (NEJM 2010, 362: 697) reported that beginning ART therapy prior to the end of TB treatment resulted in a Relative Risk and Relative Risk Reduction of ~0.5 no matter how low the CD4 count, supporting the WHO guidelines. Subsequent studies have consistently shown that the earlier ART is started after TB diagnosis the better, particularly with severely immunosuppressed patients (CD4 <50 or with otherwise severe HIV disease), immediate or within 4 weeks being better than 8-12 weeks vis-à-vis mortality (e.g. 18 vs. 27% mortality in the CAMELIA trial in Cambodia), but with twice the rates of IRIS reactions, e.g. 11-16% if within 4 weeks vs. 5-7% if 8-12 weeks). [N.B. TB meningitis may be an exception to this rule: one study of >200 patients showed no difference in mortality and increased severe adverse events with treatment started immediately vs. delaying 2 months.]

For pulmonary TB, UpToDate (9/13) provides a nice summary of this issue:

The optimal timing of integrated HIV and TB therapy is influenced by the patient's immune status. For patients with pulmonary TB and CD4 cell counts <50 cells/mm^3, "early ART" (ie, within two weeks after starting anti-TB therapy) decreases the combined risk of an AIDS-defining illness and death [61-63].

For patients with CD4 cell counts >50 cells/mm^3 in the setting of severe HIV disease (including low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or extent of disease), ART should be initiated within two to four weeks of starting treatment [62,65]. For patients with CD4 cell counts >50 cells/mm^3 in the absence of severe disease, early ART is not associated with a decreased risk of AIDS or death [61,63]; later initiation of ART (eg, 8 to 12 weeks) is associated with a lower risk of IRIS regardless of baseline CD4 cell count [61-63].

Besides immunologic status, the exact timing of ART may also depend on other clinical considerations. For example, later initiation of ART (eg, 8 to 12 weeks) may be preferred based on the patient's tolerance of TB medications and ability to swallow multiple pills. In contrast, early initiation of ART (eg, within 2 to 4 weeks) may

be considered in a patient with malnutrition or wasting, regardless of CD4 cell count. Initiating ART and TB medications simultaneously is not recommended

3. What is the risk of starting ARV treatment in this patient, and why was it delayed (beyond the WHO recommendations for a patient with a CD4 count of <50)?

- *Immune Reconstitution Syndrome or IRS. There are 2 types of IRS related to TB: 1) IRS occurring in those on active therapy – with both an initial response to TB therapy and adherence to both TB and ARV therapies documented; 2) IRS occurring in those with previously sub-clinical and undiagnosed disease, now becoming clinically obvious with immune re-activation.*

- *Almost half of patients with TB and significant immune-suppression (CD_4 < 100) have IRS with ARV initiation within 3 months, and more with disseminated TB.*

- *Given her tenuous social situation, two new diagnoses synonymous (to her) with death, drugs to take for the first time ever in a 23 year old, the high risk of IRS with a low CD4 and disseminated TB, and a gratifying response to TB treatment, ARV's were scheduled for initiation between 4-8 weeks after TB treatment initiation, longer than is recommended for the "average" patient with a CD4 below 50.*

4. What is the *differential diagnosis* in this patient, and which clinical data are for and against each possibility?

The headaches, progressive course, and (?)papilledema suggest increased intracranial pressure, probably due to a cerebral mass lesion or meningitis, and neurologic focality on exam favors a mass lesion.

The most likely possibilities in this case include: toxoplasmosis, cryptococcal meningitis with cryptococcoma, CNS lymphoma, tuberculoma (see below)…

- *Toxoplamosis: This is less likely, given the lack of symptoms at the start of SMX-TMP prophylaxis the month prior, and adherence subsequently to an effective prophylactic regimen…*

- *Cryptococcus and CNS lymphoma: Both Cryptococcus and CNS lymphoma are possible but not most likely for the same reason: either would imply a totally new diagnosis with an unusually rapid course (of about a week) for diseases which usually evolve over 1-4 weeks - cryptococcal meningitis and CNS lymphoma. (If cryptococcus, the focality on exam would suggest a complicating and even less common complication of cryptococcal infection, a " cryptococcoma", a focal mass of infection/inflammation.)*

- *Tuberculoma, on TB therapy, which has been well described (see below)*

5. What is the likely diagnosis? *Why* is it most likely? How common is it in this clinical setting? What is its pathogenesis? What are other related clinical phenomena? What are its timing and clinical features? How is it treated?

- ***Tuberculoma(s)*** *is the most likely diagnosis in this patient. While the other diagnoses noted above are clinically plausible, it is important to "construct the differential in the context of the patient", or more specifically, what one already knows the patient has - in this case, AIDS with decreased CD_4 count, and a recent diagnosis and treatment of (highly probable) disseminated TB.*
  This special clinical context makes the 4th (otherwise unusual) possibility, tuberculoma, the most likely diagnosis in this patient by far.

- *Tuberculomas are the 3rd most common CNS mass lesion in the 3rd world. They are present in 1% of all patients with TB, but 5-28% of those with TB meningitis, and up to 80% of HIV(+) patients with TB meningitis. Our patient with late-stage AIDS had no clinical evidence of TB meningitis when she was diagnosed with disseminated TB, but the two often silently co-exist: TB meningitis is seen in 1/3 of patients with miliary TB (even in the absence of neurologic symptoms), and 1/3 of patients with TB meningitis actually have widespread disseminated TB.*
  Most importantly, tuberculomas are well-reported complications in patients without prior CNS symptoms after beginning therapy for TB, either clinically disseminated TB or pneumonia.

- *Tuberculomas are thought to be a form of "TB – IRS": after initiation of TB treatment, the lymphocyte count and immune response improve (with or without co-existing HIV) and symptoms, related to the ensuing inflammatory response, can appear for the first time.*

- *Other clinical examples of "TB – IRS" are:*
  - cervical lymphadenopathy (LAD) often increases in size post-therapy (N. B. increase in cervical LAD in this patient);
  - acute respiratory distress syndrome (ARDS) has been reported after beginning treatment for miliary TB.

- *Timing and clinical features: tuberculomas post-treatment usually occur within the first 3 months of therapy, but have been reported from 10 days to 18 months later (!). Usual presenting features include seizures and/or headaches (each seen in <50% of cases), increased confusion. focal weakness, and cranial nerve deficits.*

- *Treatment is: a) continue with TB drugs; b) add prednisone for > 2 months…*

In this patient, in extremis and therefore one "can't be wrong" on admission, and without the availability of diagnostic tests, it would be reasonable to treat for all 3 infectious possibilities until a response is seen; and then withdraw treatment for the 2 less likely possibilities (cryptococcus and toxoplasmosis) while continuing treatment for the "most likely" –

tuberculoma. And, of course, monitor the patient closely (in case your analysis, decision making and empiric therapeutic strategy are wrong!).

Suggested Readings:

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Nicolls DJ, et al Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis Lancet Infect Dis 2005; 5: 795–801

Pepper DJ, et al., Neurologic Manifestations of Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: A Case Series Clinical Infectious Diseases 2009; 48:e96–107

Breen RA, et al, Paradoxical reactions during tuberculosis treatment in Patients with and without HIV Co-infection Thorax 2004;59:704–707

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

Vinnard C, et al., Tuberculous Meningitis in HIV-Infected Individuals Curr HIV/AIDS Rep. 2009 August ; 6(3): 139–145.

UpToDate (9/13) SterlingTR, Treatment of pulmonary tuberculosis in the HIV-infected patient