Introduction:

Welcome to the 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 4-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. A month 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 questions may be sent to Prof. Paccione at: gpaccion@montefiore.org

About the Author:

I'm a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York, where my career has centered on medical education for the past 40 years – as a past residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and global health advisor and program leader at the school. I've served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. I spend about 3-4 months a year in Uganda working on the Medicine wards of Kisoro District Hospital which, like most hospitals in the world that serve most of the world's population, has (almost) no resources. "At the bedside", I teach Internal Medicine residents and medical students how to assimilate the elements of history, physical exam and epidemiologic probability into a diagnostic impression that, even without definitive testing, can lead to appropriate therapeutic strategies in the field.

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63. Lumps, Worse on Treatment

A 33-year-old woman presents with 1-2 months of increasing neck lumps.

The patient went for an HIV test 6 weeks ago after feeling weak and losing weight over 4 months. At the time she did not have a cough or fever. The HIV test was positive and with a CD4 count of 150, she was started on anti-retroviral therapy (ARVs) shortly thereafter.

Despite therapy, she didn’t feel much better, and noticed that the small lumps in her neck that were painless when first noted one month prior to starting ARVs, began to enlarge more rapidly and become tender. She continued to lose weight, didn’t feel “hot” but had significant sweats at night, and did not have a cough.

Physical Exam

In no distress. Thin, with temporal wasting

- BP: 120/60
- HR: 70
- T: 37
- R: 15

Skin: normal, without plaques, lesions
Mouth: no thrush, no discolorations, no lesions
Fundi: benign, no exudates or hemorrhages
Neck: left posterior cervical chain of nodes grossly enlarged, extending to the supra-clavicular area; matted together, mostly firm with some areas of fluctuance; mildly tender, non-erythematous, not warm;
left posterior chain, top down: 8x5cm, 5x3 cm, 2x2 cm,
left supraclavicular: 3x4 cm, 2x3 cm
right side nodes: all less than 1 cm;
other nodes >1 cm in axillary, inguinal etc. regions
Lungs: clear to auscultation and percussion:
Heart: normal PMI, S1, S2; no rubs, murmurs, gallops;
Abdomen: no hepatosplenomegaly, masses or tenderness;
Neurologic: mental status, motor, sensory, cerebellum, reflexes, gait normal

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 (+), CD4 150
- ARVs recently started
- Nodes: chronic, matted/firm with areas of fluctuance
- Progressive, enlarging rapidly
- Focal and asymmetric, no splenomegaly
- Constitutional symptoms persist
2. **Name 6 descriptive features of palpable lymph nodes and the clinical significance of each feature?**

- **Size**: nodes <1 cm is most often normal and not worth investigating. Thin people often have <1 cm nodes on exam. The larger the node, the more likely its clinical significance. Studies have suggested that in chronic lymphadenopathy, node sizes >2 cm in any diameter or >2.25 cm² (1.5 x 1.5) discriminate normal vs. malignant or granulomatous pathology.
- **Mobile vs. fixed**: Nodes that are fixed to under-lying or over-lying tissue more frequently harbor malignancy;
- **Consistency**: Hard, firm, rubbery, soft, fluctuant? Normal nodes are usually “soft”. “Hard” nodes mean “rock-hard”: the word should not be used lightly – implies metastatic cancer. Infected nodes most often are “firm”, and “fluctuant” nodes imply a pus-filled center or abscess. “Rubbery” indents more than “firm” and less than “fluctuant”, and the bouncy feel implies a hematologic malignancy like lymphoma.
- **Discrete vs. matted**: Nodes that adhere to each other, i.e. “matted”, signify chronic inflammation (e.g. granulomas as in TB) or later stages of lymphomas.
- **Tender vs. non-tender**: Tenderness implies rapid growth and stretching of the pain-sensitive node capsule most often from acute (pyogenic) inflammatory processes, but tenderness can be seen with other pathologies that cause rapid nodal enlargement.
- **Location**: Generalized vs. focal: Focal lymphadenopathy is caused by lymphatic drainage of either inflammation or malignancy from a contiguous anatomic location. Knowledge of lymphatic drainage patterns is key to locate the original source of pathology. Focal lymphadenopathy also is consistent with certain types of blood-borne bacterial infections that set up discrete foci of infection and/or re-activate in one site at a time, such as TB. On the other hand, generalized lymphadenopathy is a mark of systemic inflammatory processes such as viral infections (e.g. HIV, associated with viremia at an early stage), sarcoidosis, indolent bacterial infections of the blood or reticulo-endothelial system such as subacute bacterial endocarditis, brucella or miliary tuberculosis; or diffuse “collagen diseases” such as lupus. N.B. Causes of generalized lymphadenopathy also induce splenomegaly.

3. **What are the implications of the clinical features (from history and exam) on the underlying pathology of the lymphadenopathy (LAD) in this patient?**

The main clinical features of LAD in this patient are:
- Mattred/firm with areas of fluctuance, not warm
- Chronic but progressive, recently enlarging rapidly
- Focal and asymmetric, no splenomegaly

These characteristics of the LAD suggest a non-pyogenic (too chronic, not warm), indolent inflammatory process (months duration, matted/firm) with areas of central necrosis/abscess formation (fluctuance).

Granulomatous or malignant pathology is suggested by its focality, with more rapid recent growth apparent.
4. **What is the differential diagnosis?**

- Tubercular (TB) lymphadenopathy … scrofula
- Atypical mycobacterial infection (MAI, M. scrofulaceum)
- Lymphoma
- Pyogenic infection in the neck
- Metastatic cancer

5. **What is the most likely primary diagnosis, and why?**

**What test can provide definitive diagnosis?**

*Tubercular lymphadenopathy* is most likely.

First, epidemiologic probability favors TB. HIV infection and its effect on cellular immunity has fueled the explosion of TB in Sub-Saharan Africa, with TB being the most common opportunistic infection in HIV (+) patients in Africa.

Whereas extra-pulmonary TB represents ~10-20% of all TB reported in HIV (-) patients in Africa, extra-pulmonary TB is found at presentation in 40-60% of HIV (+) patients either alone or in association with pulmonary TB. TB LAD is thought to represent, most commonly, reactivation of a quiescent focus from prior spread during the primary infection, although active mycobacteremia or lymphatic drainage from other reactivated sites of TB infection are potential origins of disease.

Even independent of HIV, TB is the most common cause of significant LAD in Africa, and LAD is by far the most common form of extrapulmonary TB (excepting pleural TB), ~40% of the total. About 70% of TB LAD involves the cervical nodes, most commonly the posterior cervical and supraclavicular nodes, although TB LAD can be anywhere – mediastinum, mesentery, inguinal, etc. In about 1/3 of patients with TB LAD more than one nodal site is involved, and in HIV disease, especially associated with a low CD4 count and disseminated disease, TB can present as generalized LAD. About 40% of those with TB LAD have associated pulmonary disease.

Clinically, the characteristics of the nodes closely fit the characteristics of chronic, infectious granulomatous pathology as noted above in question 3. Although usually non-tender due to slow growth, there can be tenderness early associated with more rapid proportionate increase in size, especially in HIV disease. Firm initially, the nodes become matted together with areas of fluctuance representing central necrosis. Draining sinuses can appear. Constitutional symptoms (fever, weight loss, etc.) are seen in only about half the patients, more commonly in HIV (+) patients.

The other possibilities in the differential diagnosis in this patient are far less likely: non-tuberculous (atypical) mycobacteria (NTM), not an uncommon cause of LAD in children, is rare in adults although seen in HIV (+) adults. NTM is far less common than TB, and remains localized to the cervical nodes, usually upper anterior chain, unaccompanied by constitutional symptoms. Lymphoma is possible, certainly in HIV (+) patients, and can become matted
(especially Hodgkin’s lymphoma). However, fluctuance is not seen and the CD4 count of 150 is high for HIV-associated lymphoma (although lymphomas associated with higher CD4 counts are more common in the ARV era). As mentioned, in our patient the course is too chronic and the nodes too cool for pyogenic infection, and they are very unlike the rock-hard nodes of metastatic cancer.

More definitive diagnosis used to rely on biopsy and demonstration of granulomas (and possibly AFB) in the lymph nodes. Biopsy and histopathology is often inaccessible to patients in rural Africa, and if available at all it’s usually only with a turnaround time of months. Genexpert PCR for TB (where available - Xpert was being rolled out to some districts in rural Africa in 2014-15 but not available in Kisoro) has revolutionized our approach to diagnosing scrofula and TB LAD. Emulsions of biopsy tissue or fine-needle aspirate yield a sensitivity of >95% in smear (+) nodes and ~70% in smear (-) nodes (specificity ~90%).

6. **What is the likely explanation for the patient’s failure to symptomatically respond to ART therapy?**
   **What are the potential ways that therapy may have influenced the patient’s presentation?**

   It is likely that the patient had unrecognized smoldering extrapulmonary TB at the presentation of her HIV disease and the onset of ART therapy.

   TB is extremely common in HIV infected persons in Africa: in some areas of South Africa, a full 25% of those in whom ART is initiated are receiving TB treatment, and another 13% will be started on TB meds in the first year of ART. TB may well have induced the symptoms interpreted as being caused by HIV in this patient since the nodes which later increased in size were already obvious when ART was started. Although generalized lymphadenopathy is commonly seen in HIV disease, in some studies in Africa up to 25% of those with later-stage HIV and generalized LAD in Africa harbored TB in their nodes.

   Therapy could have influenced the patient’s presentation in 2 ways:
   - **IRIS:** Therapy, by enhancing the patient’s immune system and ability to respond to the subclinical TB infection, induced the more florid inflammatory symptoms. This is called the “immune reconstitution inflammatory syndrome” or IRIS.
   - Side effects of the therapy given, e.g. fever, anemia, hepatitis, etc.

7. a) **What are the 2 principle therapy-associated syndromes in HIV-infected patients and what are the clinical criteria for diagnosis?**
   b) **What is the relevant differential diagnosis of symptoms beginning after ART commences?**
   c) **What is likely to have occurred in this patient and why?**

   a) Immune Reconstitution Syndrome generally presents in 2 clinically distinct patterns, well-illustrated in those infected by TB. Both patterns feature new onset or worsening symptoms of an infection after the start of ART.
1. “Paradoxical” IRIS: occurs in patients already on and responding to TB therapy who develop new or recurrent symptoms of TB after ART is started.
2. “Unmasking” IRIS: occurs in patients who are newly diagnosed with TB in the weeks following the initiation of ART.

IRIS pearls:
- Both the paradoxical and the unmasking IRIS syndromes usually present in the first few weeks - but up to 3 months - after ART is begun. The mean duration of ART before IRIS is one month.
- The median duration of IRIS symptoms is 2 months, but symptoms can last as little as a few days to up to a year.
- Paradoxical IRIS has been reported to occur in 8-43% of those started on ART after TB therapy has commenced. The incidence of IRIS is higher with more extensive TB, more severe immunosuppression, and a shorter interval between the TB and ART therapies (e.g. the incidence with ART started after 3 months of TB treatment is half that of ART started within the first 3 months).

Proposed clinical criteria (Lancet ID 2008; 8:516) (1 major or 2 minor) include:
- As “major” criteria, new or worsening:
  - Lymph nodes, cold abscesses or other focal tissue involvement
  - CNS TB
  - Serositis (pleural effusion, ascites, pericardial effusion)
- As “minor” criteria, new or worsening:
  - Fever, night sweats, weight loss
  - Respiratory symptoms
  - Abdominal pain with peritonitis, abdominal adenopathy, hepatomegaly, splenomegaly

- Potential non-TB IRIS events are very varied: they include worsening of dermatologic diseases (particularly itchy folliculitis/prurigo), genital ulcers/STIs, Cryptococcus, arthropathies;
- Although correlated with a rise in CD4 count, the CD4 response is neither absolute nor highly predictive of developing IRIS. However, the magnitude and rapidity of the drop in HIV viral load IS more highly correlated with the risk of developing IRIS than the CD4 count, as is the return of PPD skin sensitivity.

b) The relevant differential diagnosis of symptoms that begin after ART commences, which must be excluded before IRIS is diagnosed, includes:
- Failure of TB treatment because of poor adherence or resistance
- Failure of ART because of poor adherence or resistance
- Another opportunistic infection or neoplasm (particularly important if TB diagnosis was smear (-)).
- Drug toxicity
- Natural history of underlying condition not influenced by ART or IRIS phenomenon.
In this patient, as in all patients with the “unmasking” form of IRIS, the principle alternative explanation for her symptoms (i.e. failure to improve on ART and the development of obvious LAD) is simply the natural progression of either newly acquired or established TB. It is often impossible to differentiate the symptoms of expected clinical progression of untreated disease from those incurred by the “added boost” of immune reconstitution. To clarify this issue, it has been proposed (Lancet ID 2008; 8:516) that a heightened intensity of inflammatory clinical manifestations be included as a criterion for “unmasking” IRIS: e.g. florid LAD, acute respiratory distress, etc.

This patient meets this criterion, and probably had smoldering TB “boosted” by the unmasking IRIS phenomenon to ART.

8. **The patient was started on appropriate therapy for the LAD diagnosis and initially responded but then seemed to relapse with continued weight loss and overt fevers appearing, and her LAD increasing in size.**

What may explain this new clinical deterioration?

TB lymphadenopathy was diagnosed clinically, and the patient started on 4 TB medications, RIPE.

TB lymphadenopathy can progress on treatment for 1-2 months, thought to be due to a non-HIV TB-related immune reconstitution (TB-IRIS) attributed to a treatment-induced inflammatory response to released antigens, etc. Thus “IRIS” can be seen as either a response to ART directed against HIV in the presence of a “hidden” opportunistic infection OR to RIPE therapy directed against the TB itself.

Non-HIV TB IRIS is thought to complicate 2-23% of TB treatments in HIV (-) patients. In one (small) comparative study, 2% of HIV (-) patients, 7% of HIV (+) patients not on ART, and 36% of HIV (+) patients on both RIPE and ART developed IRIS. The ART-associated IRIS syndromes are both more frequent and in general more severe and multi-system than reactions to TB therapy alone.

In one review of 120 reported cases (Eur J. Clin Microbiol ID, 2002 21:803), non-HIV TB IRIS developed in 6-30% of all patients on TB therapy with a mean time of 2 months post-therapy initiation, at a new site in ~25%, and extra-pulmonary in ~80%. The CNS was the most common site of TB-IRIS reported (50%, with tuberculomas causing seizures, changes in mental status, etc), with the respiratory system next (30%, 95% of which were pleural effusions). Fever was present in 13%.

With continued therapy, the symptoms in our patient abated after 4-6 weeks, and the patient gradually gained weight and recovered.
Selected Readings:


