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 question 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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65. Getting There Slowly, Strategy and Patience

A 25-year-old woman is admitted to the hospital with 3 years of chronic diarrhea that intermittently responded to various treatments but is now worse for 3 months.

She was in her normal fully functional state of health until about 2-3 years ago when she began to have an increase in the frequency of bowel movements (BM) from her usual 1-2 times per day to 3-5 times/day. The stools were soft-watery in consistency, without blood. She had intermittent crampy discomfort but otherwise little abdominal pain, and no weight loss or fever. She received unknown therapy and improved, for ~ 6 months.

Then about a year ago, the diarrhea returned 4-5 times/day, with intermittent cramping pain sometimes waking her from sleep, with occasional blood in the stool, without mucous or tenesmus. Three months ago, she began to lose weight, feel weak, and stopped working in the fields. Pain and bloody stools increased. She was unsure of fever, but occasionally felt “hot”. She had no other symptoms such as cough, headache or joint pain. She was “dewormed” (again), and 6 weeks ago treated with metronidazole 500 mg a day for 5 days without response. An HIV test was done (her 4th since the beginning of the illness) – negative again. A Brucella antibody test returned a titer of 1:80, and she was given a diagnosis of Brucellosis and treated with Doxycycline (alone) for many weeks, without response.

She is a farmer from the area, with no exposure to lakes; is married with no children but has had 2 miscarriages; she “digs”, doesn’t own livestock and does not ingest raw milk or cheese.

Physical Exam:

Cachectic woman, lying in bed, appearing despondent.

BP: 100/70 HR: 87 RR: 20 T: 97.5 oral
Skin: no rashes; nails normal
Eyes: non-icteric conjunctiva; mild pallor; fundi benign, without exudates/hemorrhages; no lid-lag
Mouth: no thrush or cheilosis
Neck: thyroid normal, no goiter; no lymphadenopathy; no JVP/HJR
Lungs: clear to auscultation and percussion
Cardiac: normal S1, S2;
Abdomen: scaphoid, no masses or distention; mild diffuse tenderness; no hepato-splenomegaly
Rectal: (? tender, patient uncomfortable with exam); non-bleeding, non-thrombosed hemorrhoid seen;
Extremities: joints normal;
Neurologic: normal CN, mental status, motor, sensory, cerebellar, gait; no fine tremor
1. What is the “frame” of this case from the history (i.e. the key clinical features that the final diagnosis must be consistent with)?
What is the clinical significance of each?

- Young woman, HIV (-); HIV-related diarrhea and weight loss are very common in Africa (such that she’s had 4 (-) HIV tests (!)). Presence/absence of HIV orients the diagnostic approach.
- > 2 years of symptoms, diarrhea dominant: chronic intestinal disease, after 2 years of symptoms and without other manifestations, the cause is unlikely to be cancer.
- Pain intermittent, bloody stools suggest invasive involvement, possibly an ulcerating mucosa (vs. blood due to internal hemorrhoid)
- Weight loss, now cachectic: suggests either malabsorption or hyper-catabolism
- Improved after? therapy,-recurred: Was it the therapy? Or was this a placebo response? Or recurrent chronic infection? Or 2 diagnoses, one then (cured), and one now?
- Recent treatments with inadequate dosing: if the diseases treated were reasonable possibilities, their negative empiric trials were non-diagnostic, perhaps lowering their probabilities of nailing the diagnosis, but certainly not ruling anything out.

2. On admission, what overarching questions (related to the timing of her illness) complicate the construction of a “differential diagnosis” in this case?
Describe how you might go about constructing a differential and/or a diagnostic strategy.

In this patient, the important issue, unaddressed by the “frame” per se and fundamentally influencing the construction of a differential is:

- Are we dealing with one diagnosis in her past history, or more than one?
- Are all the symptoms present now manifestations of one disease that started in the distant past, or more than one?

This issue of “how many things are going on” is common in medical practice in the developing world where access to care, diagnostic resources, and medical records are limited and patients often present only when the second illness carries them over the brink.

One way to handle this situation is to formulate differentials under various assumptions, and to use in-hospital observation to further clarify the key clinical features (frame).

3. Construct a “working” differential diagnosis and briefly indicate the principle pros and cons of each disease nominated.

Assuming ONE disease process explains everything:

- Amebiasis, recurrent: ameba can cause chronic diarrhea, with blood, and be recurrent, especially if the cyst form was not treated. However, years is too long for invasive disease, weight loss and fever are not characteristic, and the stools too infrequent without mucous or tenesmus for this to be amebic “colitis”.
- Chronic infectious diarrhea: chronic forms of many acute infectious diarrheas have been identified – e.g. campylobacter, salmonella, and yersinia – which mimic inflammatory bowel
disease. Water-borne infections are so prevalent in Africa due to poor sanitation and water quality, that even such infrequent presentations of these diseases are reasonable etiologic candidates in this patient.

- Inflammatory Bowel Disease (IBD)/Crohn’s Disease: one of the major frustrations of practicing internal medicine in remote district hospitals in Africa is the inability to diagnose chronic diseases that one knows must exist in the population but can’t be diagnosed without appropriate tests that are too often out of reach (financially and geographically) for the patients affected.
  - In this case, the chronicity, recurrence, pain, bleed, weight loss, stool frequency, etc. all fit Crohn’s disease, but without colonoscopy, biopsy, pathology, or imaging Crohn’s can’t be diagnosed with confidence. Notably, there are no extra-intestinal (i.e. joint, skin, eye) manifestations to support the diagnosis, which remains a diagnosis of exclusion - of infectious etiologies.
- Intestinal tuberculosis: certainly, a possibility but less likely given her negative HIV status. Although >2 years is long, it is not inconsistent with TB of the intestines which mimics IBD, most commonly localizes to the ileum in >50% and can cause weight loss and blood in the stool. It usually is associated with fever, which wasn’t present on admission. TB can have periods of greater or lesser activity, and if TB, her prior “response” to (?) therapy may have either been to ciprofloxacin given for diarrhea or a natural (temporary) remission.
- Intestinal lymphoma: can cause pain, weight loss, diarrhea and malabsorption. However, lymphoma would be very unlikely if HIV (-), in the absence of splenomegaly or lymphadenopathy, and with >2 years of symptoms.

Assuming TWO disease processes: e.g. hemorrhoids plus…
- Giardiasis with hemorrhoidal bleeding: Most commonly asymptomatic, giardiasis is extremely prevalent worldwide. When symptomatic giardia causes diarrhea, malabsorption and weight loss without fever. “Pain” is unusual but bloating and cramps are not; recurrence is not uncommon, and the blood in the stool can be from another source now, e.g. hemorrhoids (or C. difficile complicating prior prolonged doxycycline therapy).
- Strongyloidiasis: Another extremely prevalent parasitic disease worldwide, strongyloides can cause both abdominal pain and malabsorption with weight loss. It requires therapy for longer than most parasites, at least 3 days with albendazole bid for a 50-75% cure rate, and it’s therefore likely that she could have been only partially treated when “dewormed”, explaining her recurrences. Strongyloides does not commonly cause bleeding, but rarely can, and blood could have another source, hemorrhoids or C.diff as above.
- Irritable bowel syndrome (IBS). post-infectious diarrhea: there’s evidence that IBS occurs frequently post-infectious diarrhea, thus explaining persistent GI symptoms after eradication of the infectious organism. While the blood in the stool could be from hemorrhoids, the weight loss and nocturnal abdominal pain waking her from sleep cannot be explained by IBS.

4. What is the relevance of the Brucella test in this case?

The Brucella test has little relevance in this case, but is a good example of the “have test, will order” tendency of clinicians everywhere to revere technologic over clinical data and our reluctance to employ the implications of Bayes Theorem in ordering tests and interpreting test results.

True, Brucella is a chronic, treatable disease. However, it does NOT cause an isolated syndrome of chronic diarrhea, and there is no suggestive history of occupational or environmental exposure. Thus,
the “pretest probability” is low, so low that this non-specific test should not have been ordered. Compounding the inappropriate ordering was lack of attention to the cutoff for a “positive” titer: 1/160 in low prevalence areas, 1/320 in high prevalence areas. Our patient’s titer was 1:80, thus “negative”.

[However, “positive” or “negative” labels are inappropriate cognitive short-cuts: even if considered “positive”, this low titer would be more likely to be “false positive” given the low pretest probability and likely imperfect (but unknown) test specificity in Uganda - cross-reactions have been reported with E.coli, Salmonella, and the specificity of the Brucella test is lower in patients with other febrile illnesses than in healthy controls.)

5. What diagnostic strategy/testing would you pursue?

- Microscopy for ova and parasites: looking for ameba, giardia, strongyloidies. Unfortunately, microscopy would likely be low yield for any of these diseases in this case (sensitivity in the best of circumstances ~50% per (properly prepared) stool specimen, and in a rural district African hospital, probably lower.
- Look at the stool! Is there blood, mucous? If blood, are the hemorrhoids seen on the admission rectal exam actively bleeding? Hemorrhoids are common, especially in people with chronic GI disorders. Their presence does not mean they are the source of the blood unless they are actively bleeding at the time of the exam.
- Follow exam closely, and get a better sense of a) pain and b) fevers – are there any?
- Series of empiric trials of anti-parasitic agents, and antibiotics (N.B. No cultures available) withholding ciprofloxacin which has activity against TB.
- CXR, looking for evidence of co-existing active pulmonary TB, in the past seen in 90% of patients with intestinal TB, now, from studies in the post-TB-antibiotic era, in the wide range of 10-90%.

In the hospital after admission:

- Microscopy of two stool samples was negative for ameba, giardia, and strongyloidies.
- The stool was observed to be soft-watery, with specks and streaks of blood.
- Homespun “anoscopy” was performed with a lubricated plastic test-tube and a flashlight immediately after blood was seen in the fresh stool: it showed NO evidence of active bleeding from the external or internal hemorrhoids. Conclusion: blood is originating not from hemorrhoids but from the intestinal mucosal disease causing the pain and weight loss.
- Temperatures were measured 3-4 times/day: a low-grade fever of 100.5 orally was noted the next day.
- Empiric therapy with metronidazole 750 3x/d for a week was started, covering both ameba and giardia (and even C.Difficile).

Somewhat surprisingly, after 5 days of treatment with metronidazole the diarrhea significantly improved to 1-2 loose stools/day with occasional blood, but fevers of 101.5-103 daily (of which the patient was wholly unaware) were documented daily after the first days of treatment.

What could have explained this response to treatment?
The resolution of the diarrhea on metronidazole might have strengthened the possibility of either giardia or ameba as the cause of the problem, but the fevers were inconsistent with either diagnosis. Likewise, *C. difficile* successfully treated is possible, but the fevers only seemed to increase as the diarrhea resolved, and the patient felt no better, so it couldn’t have been the whole story.

Another plausible reason for the response to metronidazole could be suppression of bacterial overgrowth which could have been causing malabsorptive diarrhea behind partial obstruction(s) in the intestines, without influencing the cause of the obstructions – the responsible disease itself.

Occasional abdominal pain persisted, no cough or sputum developed, the urinalysis was unremarkable, and the exam didn’t change.

A chest X-ray (for TB) was clear.

The next initially planned empiric trial of albendazole for strongyloides was withheld given the fevers (which Strongyloides does not cause, unless in the context of hyperinfection). Instead, antibiotic therapy with ceftriaxone and erythromycin as empiric treatment of chronic salmonella or campylobacter infections was begun. After a week, there was no change in the fevers or in-patient well-being.

6. What is your next step?

Empiric therapy for Tuberculosis.

In the pre-imaging era when TB was still seen in the U.S. (but waning in prevalence), TB accounted for a third of “Fevers of Unknown Origin”. Of note, these were difficult cases, diagnostic dilemmas, and identifying the locus of the infection was a challenge. Often, the last phase of the diagnostic work-up for an FUO was simply empiric therapy for TB.

Diagnosis in most areas of rural Africa is still in the “pre-imaging era”, and TB is far more prevalent now in Africa than in the U.S. of the 1950-60’s when the classic FUO data were collected and reported.

Genexpert PCR may change things where available, but as of early 2015 the data for Xpert diagnosis of intestinal TB from samples of stool were scant. 3 studies with a total of fewer than 20 patients showed 100% Xpert sensitivity of stool samples for diagnosis of pulmonary TB (swallowed sputum), but nothing on intestinal TB without pulmonary involvement.

In our patient, TB treatment was begun -- without any response for the first few days. However, by the end of the first week of therapy the fevers were lower, and during the second week of treatment the patient became afebrile. She progressively gained appetite and strength, remained afebrile without diarrhea or abdominal discomfort, and weeks later, when seen in the clinic, had gained weight and was back working in the fields.

7. How does the diagnosis, only apparent after correct empiric therapy was tried, explain the patient’s presentation and course of illness?
This case illustrates the illusive nature of extra-pulmonary TB, particularly in the district hospitals of the developing world without advanced imaging, biochemistry, or microbiology. Although it is quite likely that she had TB from the response to empiric TB therapy, there were a few “curveballs” that make it difficult to be sure exactly where the infection was, what explained the remission for 6 months over a year ago, and why the diarrhea responded to metronidazole (although overgrowth is a likely explanation, see below).

Since therapy for TB is of long duration with many drugs and costly, unless the patient seems terminal, other possibilities in the differential are usually targeted for empiric therapy first.

Our patient probably had TB of the intestines, which has a predilection for involvement of the terminal ileum (like Crohn’s Disease) with a mass or tenderness localized to the right lower quadrant (which she didn’t have).

Intestinal TB can cause weight loss (40-90%) through both hypercatabolism and malabsorption and is one of the few causes of malabsorption that is associated with fever. (Of note, patients with TB are often unaware of the fevers they are having, as was this patient.)

The malabsorption is multifactorial - seen in 50-70% of patients with evidence of obstruction from intestinal tuberculomas, and 25-40% without obstruction – and is due to bacterial overgrowth most commonly (likely in our patient who responded to metronidazole), bile salt deconjugation by bacteria and malabsorption by the diseased ileum, decreased absorptive surfaces, and lymphatic involvement.

Intestinal TB also causes pain in 80-90% - colicky due to peristalsis against obstructing lesions or constant with mesenteric lymph node involvement; fever (40-70%, only!); diarrhea (10-20%, which our patient had, probably due to malabsorption).

Suggested Readings:

Sharma MP, Ahuja V., Abdominal (Gastrointestinal tract) Tuberculosis in Adults, in H. Simon Schaaf, A Zumla; Tuberculosis: A Comprehensive Clinical Reference 2009, Saunders


Tanoue LT, Mark EJ, Case 1-2003: A 43-Year-Old Man with Fever and Night Sweats NEJM 348 (2): 151 – 161

Maynard-Smith L, et al Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review BMC Infectious Diseases (2014) 14:709