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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An 80-year-old woman is carried to the hospital too weak to walk, complaining of cough and stomach and back pain for “over a week”.

For the past year she has been declining. About 2-3 times per month she has sought medical attention for sundry complaints similar to her presenting illness - diffuse abdominal and back pains, intermittent diarrhea, sometimes fevers and sweats, and a mostly non-productive cough with occasional white sputum. She has received malaria treatment frequently as well as courses of antibiotics with occasional response, but the sickness keeps recurring a week or two later. She’s had decreased appetite and been losing weight for 2 years while living with and being cared for by her daughters. She and her daughters say that she has not been feeling unusually sad or depressed. She has never smoked.

This time she is weaker than usual and the abdominal and back pain and the cough seem worse. She has had no fevers recently. She comes to the hospital carried by her concerned daughters seeking another opinion and “different medicines”.

**Physical Exam:**

Sitting on the bed, gaunt, cachectic and tired appearing, in no acute distress

T: 92 p.o, repeated, 93 F rectal; BP: 70/45 lying, 65/40 sitting; HR: 80 to 95 sitting; R: 28

Skin: dark, particularly face and back of her hands; no rash
HEENT: no thrush, no proptosis/lid lag; fundi normal;
Neck: supple, no lymphadenopathy, thyroid normal without goiter; no JVP/HJR
Breasts: normal, without masses
Lungs: right base, dullness to percussion and tubular breath sounds without crackles; otherwise clear
(patient says she is “too weak” to cough)
Heart: normal PMI in 5th ICS, MCL; S1, S2; no murmurs
Abdomen: no masses, no hepato-splenomegaly; no tenderness; normal bowel sounds
Extremities: no edema, cyanosis, clubbing; pulses weak but palpable
Neurologic: slow mentation, difficult to assess mental status; sensory (pin, vibration, position) intact; cerebellum, cranial nerves intact; reflexes +2 diffusely; motor: diffusely weak, 5-/5; no fine tremor of outstretched hands; gait weak, slow, not broad-based
1. What is the “frame” of this case (the key clinical features the diagnosis must be consistent with)?

- 80-year-old woman, slow deterioration over 1-2 years
- “Recurrent” illnesses, 2-3x/month
- Weight loss, cachexia
- Cough
- Non-specific symptoms of diffuse pains, diarrhea
- Not acutely ill

2. Identify and explain briefly the clinical significance of 6-10 key features of the physical exam, both positive and negative, given the patient’s complaints?

- Cachexia: corroborates the history of weight loss over 1-2 years and suggests a chronic illness. In rural Africa where endemic poverty is often compounded in the elderly by loss of ability to work and social support (if children have migrated to the city or died of AIDS), the resulting malnutrition plus normal loss of weight in old age can make “cachexia” poorly predictive of additional biologic disease. However, in this case, the degree of cachexia and an intact social network suggest that an underlying disease is responsible.
- Hypotension, hypothermia: Although each can be seen in severe malnutrition, the combination is worrisome and consistent with infectious and/or endocrine etiologies (e.g. adrenal insufficiency, myxedema).
- HR of 80 despite low BP: consistent with either chronicity of the hypotension, lack of responsiveness to catecholamines, and/or hypothermia-induced bradycardia.
- Respiratory rate of 28: suggests either a pulmonary process, and/or acidosis.
- No thrush or skin rashes: no suggestion of underlying HIV on exam
- Dark skin in sun-exposed areas: possible clue to underlying Addison’s disease, or B12 deficiency in Africans.
- No lymphadenopathy or hepatosplenomegaly: sometimes LAD or organomegaly is seen in disseminated TB, a common cause of insidious decline in elderly Africans;
- No goiter, HR <90 supine, no tremor: Either hypothyroidism or “apathetic” hyperthyroidism can explain chronic failure to thrive in the elderly. Hypothyroidism can cause hypothermia but not hypotension; hyperthyroidism will often manifest a fine tremor and HR>90; both will cause goiter. In this patient, there’s no evidence of thyroid disease on exam.
- Lungs: dullness and tubular breath sounds at right base: suggestive of a consolidating pneumonia. This would explain the increased RR. The absence of acute distress by history or on exam is far more consistent with a chronic pneumonia caused by TB than a consolidating pyogenic pneumonia caused by pneumococcus.
- Abdominal exam: no tenderness despite complaints of pain: more consistent with a physiologic cause of non-specific pain than an anatomic one, such as inflamed viscera.
- Mental dullness and generalized weakness: consistent with a hormonal or electrolyte imbalance.
- Normal peripheral neurologic exam, sensory, cerebellar, gait…. Not suggestive of B12 deficiency.
3. Which exam finding should be followed by more in-depth questioning and more focused examination? Specify the question(s) and the additional findings to be sought.

- The dark skin noted in sun-exposed areas may be normal or may be a sign of Addison’s Disease/hypoadrenalism - a disease consistent with many of the nonspecific symptoms and exam findings in this patient and a rare complication of TB. The hyperpigmentation characteristic of Addison’s, due to the increased levels of melanocyte-stimulating hormone and ACTH, is often missed in dark-skinned people where it is considered a variant of normal.
  - B12 deficiency has also been associated with darkened skin in Africans – thus the importance of a careful neurologic exam and a CBC and peripheral blood smear.
- When the family was asked whether “there were any changes in her skin” (open-ended inquiry is essential to avoid bias in the response) all 4 adults around her bed immediately chimed in that her face had become “much darker”, and one daughter followed up with: “she stays inside all the time now, goes out in the sun rarely and yet she’s still much darker”. Such spontaneous information is highly credible. (N.B. The next, more closed but still open-ended inquiry would have been, “has her skin color changed over the past year, and if so, how?”, but it wasn’t necessary.)
  - Comparison with other family members may also be helpful.
- A focused exam for hyperpigmentation should include inspection of sun-exposed areas (thus face and back of hands), areas of friction – elbows, knuckles, spine, knees and the buccal mucosa (towards the back of the lips where lips meet teeth); the creases of the hand, scars, and nailbeds. (Scars that develop during the period of adrenal insufficiency are hyper-pigmented, although older scars that developed earlier don’t get darker.)
  - In females, in whom androgens come from the adrenals, loss of adult body hair is also a sign of adrenal insufficiency.
- In this patient, the buccal mucosa and knuckles were hyperpigmented, and body hair was sparse (but she was an 80-year-old African woman).

4. Identify some of the primary, broader “meta-diagnostic” questions - the differentials for which are concepts or processes and not diseases - that are germane to this patient’s presentation?

What are the relevant differential diagnoses appropriate to each?

Two primary diagnostic questions are:
- What’s the physiology behind the patient’s recent illness marked by hypotension, hypothermia and weight loss?
- Is this all chronic or acute-on-chronic? i.e. Is this presentation a late stage of one chronic process, or an acute disease complicating a chronic one?

The potential physiologic mediators of her present illness are three:
- Volume depletion: how much of the hypotension can be explained by volume loss?
  - (Volume loss is not suggested by the history, but the patient did have diarrhea and perhaps had low oral intake).
- Re-distributive shock induced by catabolic inflammatory mediators (e.g. cytokines) released in response to infection, either chronic and/or acute-on-chronic
• Absence of the adrenal hormones necessary for maintenance of blood pressure, energy utilization and storage, and overall well-being.

As for chronic vs. acute-on-chronic, the specific diagnostic issues suggested by the exam are:
• Are we seeing the late presentation of a chronic process such as pulmonary and disseminated/miliary TB, or is there something else - such as sepsis or volume loss - that’s causing the hypotension?
• b) Is the patient’s chronic deterioration caused by insidious cytokine-driven catabolism seated in the lung - either infectious or neoplastic, and possibly disseminated - or a related metabolic process such as adrenal insufficiency, hyponatremia or hypercalcemia?

The differential diagnosis of the lung process includes:
• TB: causing weight loss, failure to thrive, cough and tubular breath sounds on exam
  o (If she were HIV positive, other chronic infections would enter the picture - such as Cryptococcus, but in that case other skin or CNS symptoms/signs might be expected - or lymphoma or Kaposi’s Sarcoma for which there is no other evidence on exam.)
• Neoplasm: less likely than TB in Africa, especially in a non-smoker without other evidence of metastatic disease after more than a year of weight loss.
• Acute pyogenic pneumonia: unlikely given the patient’s history and non-acute presentation.

If Addison’s is complicating the presentation, the differential would include:
• TB: by far the most likely cause of Addison’s in Africa is TB
• Other etiologies of Addison’s include:
  • Fungal disease when disseminated, such as Cryptococcus or histoplasmosis (both seen in East Africa, but histoplasmosis rarely causes clinical disease);
  • HIV-related: CMV, cryptococcus, MAI, HIV itself; or
  • Neoplasm: lymphoma, breast or lung cancer.

5. In African district hospitals, certain provocative maneuvers, observations and simple labs can help diagnose the physiologic derangements considered here. What are the physiologic explanations for the following observations in this patient, and what another maneuver is called for?

BP became unmeasurable when the patient stood up, and the HR increased to 130; 500cc NS over 15 min led to a BP increase of only 5mm systolic, to 75/45 which, within 30 minutes, returned to its baseline 70/45 supine.

A urinalysis on admission (before fluids) showed a clear urine with a specific gravity of 1.010, which didn’t change with the fluid administered. No casts or cells were seen. The patient excreted all fluid administered promptly, with the urine remaining isosthenuric and the BP ~65-70/40-45.

… and one other maneuver was done, and confirmatory result was obtained…!? 
(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 would be expected to be 75-100 baseline.)

There are no cortisol or electrolyte levels to measure in district hospitals, so a diagnosis of hypoadrenalism depends largely on clinical observation and the response to empiric therapy with fluids first, and then with steroids.

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

- **Blood pressure:** in the case of adrenal insufficiency or sepsis causing hypotension (septic shock), IV fluid will not lead to a significant increase in BP; however, if the hypotension is due to uncomplicated volume depletion, there should be a rapid rise in BP with a “fluid challenge”. When used as a diagnostic test for shock, saline must be given quickly, as a measurable IV bolus, so all fluid stays in the plasma space for the diagnostic assessment, while the examiner assesses the acute response of the 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.
  - If the BP fails to respond to a correctly performed fluid challenge, the administration of IV steroids should help differentiate between septic shock and Addison’s/hypoadrenalism. In sepsis, the BP will not respond acutely, while in Addison’s, IV steroids may lead to an unambiguous increase in blood pressure within minutes to hours.

- **Urinalysis/urinary concentrating ability/response to fluids:** due to renal tubular dependence on cortisol, a patient in acute adrenal crisis cannot concentrate his urine even when volume depleted, and the urine will be isosthenuric. The patient is not able to retain the fluid administered which will be promptly excreted, the blood pressure will respond minimally, and the patient will become polyuric while in shock (“hyperdynamic shock”).

In volume depleted patients, the initial urine will be concentrated, and become less so as fluid is administered and urine output increases.

Septic shock may be complicated by acute tubular necrosis (ATN), which will have isosthenuric urine with casts, and oliguria which will respond only minimally to fluids.

**Additional Maneuver:** IV hydrocortisone 50 mg was administered, and within 20 minutes the BP rose from 65 to 80 mm.Hg, and by the next day the patient felt much better, taking her first spontaneous unassisted steps.

Given the high “pre-test probability” of Addison’s Disease in this hyper-pigmented chronically ill patient, the above blood pressure and urinary responses to fluids and steroids were interpreted as confirming Addison’s disease.
6. What other tests would be appropriate in this patient?

- Sputum for AFB: 2-3 sputa for AFB are approximately 60-80% sensitive for diagnosing co-existing pulmonary TB, suggested in this patient by the history of cough and the lung exam.
- Genexpert PCR of sputum, unavailable at the time, could have been very helpful in this case with a sensitivity of 95% in smear (+) patients, 60-70% in smear (-) patients, and a specificity of 98%. If the patient can produce only scant sputum or saliva, the sensitivity in smear (-) cases drops to the 30% range but can still be helpful.
- HIV test: important in all patients in Africa with suspected TB, especially extra-pulmonary TB and/or Addison’s Disease. A positive result would broaden the differential of Addison’s disease beyond TB.
- CXR: not necessary if the AFB smear (or Genexpert) is positive, but appropriate (if available) if the sputum exam is negative.
- Abdominal X-ray: looking for signs of adrenal calcification suggestive of TB
- CBC: for suggestions of B12 deficiency as the cause of hyperpigmentation and slow mentation, either cytopenias, ovalocytes, hypersegmented neutrophils, or large MCV may be clues.

In this patient:
- She was too weak to produce sputum for AFB exam.
- The HIV test was negative.
- The CXR showed an alveolar right lower lobe consolidation without a cavity.
- Abdominal film showed speckled calcifications above right kidney;
- The CBC showed a Hb of 10, normal WBC and platelets, and an MCV of 84 with an RDW of 13.8... not suggestive of B12 deficiency

7. Describe your treatment strategy for this patient and how the possibility of two diagnoses may complicate its interpretation. Are there any drug effects to be mindful of in diagnosing and/or treating patients with one or both diseases?

The diagnosis of Addison’s Disease complicates the usual diagnostic/treatment algorithm for smear-negative TB in HIV negative patients. The usual strategy (in HIV negative patients) involves treatment of pyogenic pneumonia and monitoring the response to therapy before concluding that the consolidating pulmonary process (in non-responders) is indeed TB requiring 6 months of directly observed therapy. In this patient, steroids must be given to treat the Addison’s, particularly in stressed-infected patients as sick as this one, and steroids will mar the interpretation of the empiric antibiotic therapy.

Since TB is the (overwhelmingly) likely cause of both the chronic (by history) pneumonia and Addison’s Disease in Africa, treatment for TB along with chronic steroids should be administered.
Although unlikely and not “required” as an explanation for the patient’s presentation, since there’s no room for empiric error in this hypotensive/hypothermic elderly patient, treatment of an additional super-infection by a bacterial organism is wise.

Rifampin causes increased metabolism of steroids and thus can precipitate an adrenal crisis in compensated hypoadrenal patients. Other medications that increase steroid metabolism and can precipitate hypoadrenalism are the anti-epileptics, phenytoin and Phenobarbital.

8. How commonly do the diseases considered in this patient coexist? To what degree do their symptoms overlap and are there any symptoms that signal that both diseases might be present?

Addison’s Disease, symptomatic or clinically overt hypo-adrenalism, is a rare complication of tuberculosis, occurring in fewer than 5% of patients with TB in most reports. However, since 90% of the adrenals must be destroyed before symptoms occur, lesser degrees of hypoadrenalism, i.e. impaired reserve assessed by a subnormal response to ACTH stimulation, is much more frequent: one study of 50 patients from Tanzania with pulmonary TB documented an impaired response to ACTH in 16 of them, 2 of whom were overtly Addisonian. Patients with an impaired response to ACTH, i.e. partially adrenally insufficient, are precisely the ones in whom the use of medications that increase steroid metabolism or the stress of another infection can precipitate an overt Addisonian crisis.

Despite the infrequency of Addison’s in TB, TB is the by far the most common cause of Addison’s disease in the developing world, causing over 70% of the cases in Africa. This mirrors the situation in the West prior to 1950 when TB caused 70-80% of the cases of Addison’s. (Now in the West, where TB has largely disappeared (except in immigrants) and subsequently a rare disease (Addison’s) has gotten rarer, TB causes less than 20% of the cases of adrenal insufficiency. Nowadays, 80% of Addison’s cases are caused by autoimmune adrenalitis. A TB etiology is often suspected when abdominal CT demonstrates enlarged or calcified adrenals instead of the adrenal atrophy of autoimmune disease, and is confirmed by biopsy demonstrating AFB, granulomas, or caseation necrosis.)

Unfortunately, both TB and Addison’s disease cause similar symptoms: weight loss, lethargy, loss of energy, anorexia and non-specific failure to thrive being the most frequent. The Tanzanian study found only a statistically significant lower diastolic BP in hypoadrenal-TB patients than non-hypo-adrenal TB patients: 64 vs.74. (Our patient had a DBP of <50).

However, the diagnosis may be suggested by a composite constellation of other hypoadrenal symptoms such as salt-craving, frequent abdominal complaints of nausea/vomiting, pain and diarrhea; diffuse musculo-skeletal aches; psychiatric changes such as depression/psychoses/mental dullness and/or exam signs such as hypotension that fails to respond to fluid administration, change in skin pigment and loss of body hair in females. Further investigation as outlined above may then help strengthen the diagnostic suspicion enough to warrant a steroid trial.

Of note, most cases of Addison’s due to TB are irreversible (though not all, especially if the infection is active and early), so treatment with steroids needs to be continued for life in most patients. In this TB-infected patient, it makes sense to start with a stress dose of 100 mg
hydrocortisone, followed by the equivalent of 50 mg of hydrocortisone daily for a week, tapering to 25-30 mg through the 6-8 month course of TB RIPE (rifampin) therapy, and then to ~20 mg/day maintenance thereafter.

Suggested Readings:

Alevritis EM, et al., Infectious Causes of Adrenal Insufficiency SMJ 2003; 96 (9): 888
Keljo DJ, Squires RH  Just in Time  NEJM 1996; 334:46