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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67. The Muffle of an Oft-Forfeited Cure

A 32-year-old male, a farmer from a village around Kisoro, presents with 2 months of increasing weakness and weight loss, with recent development of shortness of breath. He was well until about 2 months ago when he began to get fatigued before finishing a day’s work. He lost his appetite and started losing weight, developing an intermittent dry cough without sputum and occasional diarrhea without blood or mucous. He experienced neither fevers nor sweats. About 4 weeks ago, he noticed lumps growing in his neck, non-painful and non-tender, on both sides.

Around that time, his legs began to swell at the end of the day. Over the past 2 weeks he’s gotten progressively shorter of breath while walking home from the fields, and his belly has become slightly distended. He has had no problems sleeping or breathing while lying flat and has had no sweats at night. His mild cough has persisted without sputum but has not worsened. He has had no chest pain.

He has been healthy his whole life, without chest or joint pains as a child or breathing difficulties. He’s the father of 3 healthy children aged 2 to 6 years old, and lives with his family. His wife is healthy, and digs. He previously worked as a migrant farmer around Kampala, but not since marriage 7 years ago and he has had no extramarital affairs.

Physical Exam:

In no distress, sitting up in bed, lumps visible in his neck

BP: 110/70   HR: 115   T: 97.9 p.o.   R: 24, non-labored

Skin: normal, without rash
Conjunctiva: normal, non-icteric, no petechiae; fundi: benign, no papilledema or exudates
Mouth: no thrush or violaceous plaques
Neck: lymphadenopathy bilateral submandibular, posterior cervical, supraclavicular, firm, non-tender, discrete, not matted, 1.5-2 cm; no goiter; trachea midline
JVP sitting to 1-2 cm below jaw, diffuse triphasic pulsation, no cannon waves seen; +HJR
Lungs: left side dull to percussion with decreased breath sounds ¼ up, egophony above dullness
No crackles, right lung clear
Cardiac: PMI palpable and visible 2 cm lateral to mid-clavicular line, 2 cm in diameter, no RV lift nor LV heave;
heart sounds diminished, S1, S2 heard, without S3, S4 in left lateral decubitus position;
bi-phasic near-continuous sound heard at the apex and left sternal border …
Abdomen: slightly distended when lying supine; +shifting dullness; bowel sounds normal non-tender without rebound or percussion tenderness except over RUQ
RUQ tenderness to percussion and gentle punch; liver percussed 13 cm in span, 7 cm below costal margin
Extremities: +2 pitting edema to mid-shin bilaterally; warm peripherally
Neurologic: intact mental status, cranial nerves, motor, sensory, reflexes, cerebellum, gait
1. What is the “frame” of this case from the history and physical exam? (i.e. the key clinical features the final diagnosis must be consistent with), and the clinical significance of each feature noted?

- Young, previously healthy - suggests no prior lung, cardiac or liver disease, common causes of edema.
- Insidious progression over 2 months with weight loss - is consistent with a chronic infectious or neoplastic etiology, i.e. a catabolic illness.
- Lymphadenopathy, edema, dyspnea, cough – indicative of multi-system involvement.
- Heart rate 115 and BP normal, while afebrile with warm extremities – indicates that the resting tachycardia is not due to fever or shock, common causes of tachycardia.
- Large heart with decreased heart sounds, and near-continuous sound heard at apex/LSB – see below.
- Pulmonary dullness and decreased breath sounds – suggests pleural effusion.
- JVP, edema, shifting dullness, tender RUQ - these are signs of increased RV pressures causing congested liver, ascites, edema.

2. What is the differential diagnosis of a “near-continuous sound” at the cardiac apex, and how do the abnormalities mentioned produce the sound described?

A continuous (or near-continuous) sound either means two back-to-back murmurs spanning systole and diastole, or two surfaces rubbing together as the heart contracts and relaxes. Thus, in this case, the biphasic near-continuous sound suggests either a

- Biphasic murmur e.g. MS/MR or AS/AI, or flow through a shunt as in a patent ductus arteriosus which would be best heard towards the base of the heart
- pericardial friction rub, which can have one, two or three components. The 3 components are, in descending order of frequency, 1) ventricular systole; 2) atrial systole; 3) ventricular relaxation. 15-20% of rubs are monophasic (just ventricular systole), 30% biphasic (ventricular and atrial systole) and 50% are triphasic with all 3 components present.

3. By physical exam, how are the diagnostic possibilities differentiated?
   Which is most likely in this patient from the clinical history? Why?

- A pericardial rub is “scratchy”, “grating”, “sandpaper”, “close to the ear”, and variable – coming and going;
- A pericardial rub can change dramatically with patient position. The rub is caused by friction between the opposing visceral and parietal pericardial surfaces. Positional change, which alters the spatial relationship between the two surfaces and the weight of the heart beating on the pericardium, influence the duration and intensity of the rub. Rubs are usually loudest near the left sternal border in the 3rd-4th ICS when the patient is sitting, leaning forward. In about a third, the rub is accentuated during inspiration. Most murmurs don’t change appreciably with position (although asymmetric septal hypertrophy or mitral valve prolapse may).
By history, the 2-month evolution of progressive symptoms in a previously well, 32-year-old man strongly augers against the dyspnea and edema being caused by heart failure from valve dysfunction. Cardiac symptoms from AS/AI, MS/MR or intra-cardiac shunts would usually evolve over many months to years.

In this patient the near-continuous biphasic sound was indeed “scratchy”, like rubbing 2 sheets of sandpaper together, and “close to the ear” as if originating right beneath the stethoscope. It also became louder and longer when the patient sat up and inhaled, and one component almost disappeared in the right lateral decubitus position.

4. a. Disease of which tissue is causing the near-continuous heart sound?
   The likely “tissue-level” diagnosis is pericardial effusion/pericarditis.

   b. Which findings are consistent with this pathologic process in this patient?
   Consistent with pericardial effusion/pericarditis in this patient are:
   - HR>100: found in 70-100% of patients with pericarditis (in Africa)
   - Decreased heart sounds: ~85%
   - JVP elevated: in 15-60%
   - Ascites: 10-70%
   - Liver>4cm below costal margin: (up to) 90%
   - Edema: ~60%

   c. The absence of which symptoms and signs auger against this process, and how strongly?
   Against the classic picture of pericarditis in this patient are:
   - No chest pain: NO chest pain is reported in up to 75% of patients with (TB) pericarditis
   - SBP >100: normal BP is seen in 50-90% of those with pericarditis in Africa
   - PMI palpable and displaced: a palpable PMI is seen in ~50% of pericarditis/effusion in Africa

   d. What is the principle pitfall made by bedside clinicians considering this diagnosis?
   The principle diagnostic pitfall for bedside clinicians considering this disease is not fully appreciating that most of the “classic” findings that we associate with pericarditis/effusion are neither sensitive nor specific.

   Depending on the series, most symptoms/signs are variably reported to be present in 20-70% of those with symptomatic pericardial disease. Thus, anything can fit, and few findings can confirm or rule out the diagnosis. Differences between case series depend largely on referral and selection spectra, access to care and technologic diagnosis, HIV prevalence, etc. - all of which boil down clinically to the degree of illness and stage of disease at presentation of the average patient in the reported series.

   e. Explain the importance of the near-continuous heart sound vis-à-vis the diagnosis and management of this patient?
A diagnostican should always be attuned to clinical findings whose high specificity most narrows the differential diagnosis or more efficiently focuses diagnostic or management efforts.

A pericardial rub is one of these findings: it narrows the differential to a finite spectrum of diseases most of which can be diagnosed with a fair degree of certainty by epidemiologic probability and/or other associated clinical features; and it has significant management implications vis-à-vis both treatment and monitoring for complications.

f. How commonly is this auscultation finding heard in patients with this disease in Africa? What are the most consistent/reliable findings that should alert the clinician to think of this disease?

A pericardial friction rub is heard in <30% of cases of pericarditis/effusion in most series from Africa, and tamponade, associated with large effusions, does not significantly decrease its frequency.

That’s VERY SOBERING! Since the majority of patients with clinically significant pericarditis/effusion do NOT have a rub, when then should the diagnosis be suspected?

The most consistent/reliable findings in series of (mostly TB) pericarditis are decreased heart sounds, heart rate >100, and hepatomegaly – each is seen in >80% of reported cases.

Also, in rural Africa patients are thin, and “sick” anorectic patients with high respiratory rates might be expected to be volume-depleted with low central venous pressures and absent neck vein pulsations: therefore in the appropriate clinical context, lack of a visible or palpable PMI or presence of neck vein pulsations visible with the patient sitting (even if low in the neck), each of which is seen in only ~50% of patients with clinically significant effusions, should suggest the diagnosis of pericardial disease.

On the other hand, a murmur of TR or MR or an EKG that demonstrates left axis deviation support myocardial over pericardial disease.

Essentially, every patient with a new diagnosis of “CHF” should be carefully assessed for the presence of pericardial disease, and the entire spectrum of symptoms, exam signs and EKG-imaging results critically reviewed before this often-treatable diagnosis is eliminated from consideration.

5. Which important Physical Exam signs (which should be routinely assessed in every patient with dyspnea and/or edema) are not reported in the vignette above?

- Cardiac percussion is a useful technique in assessing cardiac enlargement. Normal hearts are < 10.5 cm from mid sternum; its sensitivity for cardiac enlargement is >95%, though it’s only ~60% specific at this cutoff; in significant pericardial effusions, the area of cardiac dullness extends to the right of the sternum in over 90%.
• Pulsus paradoxus: this is an important sign to follow daily in any patient with pericardial disease. 98% of patients with cardiac tamponade (in which cardiac output is compromised by the effusion) manifest pulsus of >12 mmHg (specificity of 83%, LR+ 5.9, LR- 0.03).
• Of note, neither a normal BP nor the presence of a rub strongly mitigate against a diagnosis of tamponade.

In this patient, the heart was percussed 12 cm. from the mid-sternum, and dullness extended to the right of the sternum. He had a pulsus of 7-8 on multiple determinations.

6. Which social and epidemiologic realities of Africa influence consideration of the likely etiology of the disease process (“process X”) affecting this patient?

Pericarditis is a relatively uncommon disorder, but a prime example of the influence of poverty and the prevalence of HIV in determining disease probabilities.

Africa influences the etiologic probabilities in 2 ways:

  1) Extreme poverty breeds widespread Tuberculosis (95% of all the 10 million cases of TB annually come from Asia, Africa or Latin America, as do 98% of the 2 million deaths per year);
  2) Africa’s epidemic of HIV: on the one hand, HIV increases the prevalence of both pulmonary and extra-pulmonary TB and, on the other, broadens the pool of possibilities of other causes of pericarditis.

7. a) What is the (etiologic) differential diagnosis of Process X in Africa and how does it contrast with the West?
   b) How would the differential be influenced if he were HIV (+)?

   a) Two representative articles in the last 10 years demonstrate the contrast between Africa and the developed West vis-à-vis pericarditis etiologies:
   • In Africa, Reuter el al (QJM 99:827, ’06) reported a series of 233 patients from South Africa between 1995-01 with the following disease prevalence: Tuberculosis 70%; neoplastic 10%; autoimmune 5%; septic 2%; idiopathic/other 14%
   • And from Italy, Imazio et al reported a series of 453 patients (Circulation 2007, 115:2739): “idiopathic/other” 83%; neoplastic 5%; autoimmune 7%; tuberculosis 4%, septic 1%.

   b) Tuberculous Pericarditis: This is by far the most likely etiology of pericarditis in Africa, over 70% of all cases, and over 90% of cases of pericarditis in HIV + patients. TB involves the pericardium through retrograde lymphatic spread from nodes in the mediastinum or less commonly through hematogenous dissemination, and most of the effusion and damage are due to the ensuing hypersensitivity reaction to the tubercle bacilli. It usually presents insidiously, with symptoms developing over weeks. Of interest, it’s the second most common cause of “CHF” in South Africa, after rheumatic heart disease (more common than hypertensive or dilated cardiomyopathies). 1-8% of all cases of pulmonary TB in Africa are reported to involve the pericardium.
- Neoplastic pericarditis: neoplasms metastatic to the pericardium include breast, lung, melanoma, lymphoma and sarcoma. Usually these cancers are obvious on physical exam or by history, particularly in Africa where patients’ access to care is delayed.
- Autoimmune diseases: SLE, rheumatoid arthritis, scleroderma, etc. can all cause pericarditis but usually as part of a broader rheumatic/connective tissue presentation.
- Septic pericarditis: rare, usually due to strep or staph from another source, acute and progressive over days to a week usually; more commonly associated with pain, fever (median>102), and EKG changes; and lethal without prompt open drainage.
- Other non-infectious etiologies: uremia and radiation pericarditis are seen commonly in the West, but not in Africa. Uremia would be possible however if accompanied by a compatible spectrum of other uremic symptoms (not seen here).
- Other infectious etiologies: In the West, the most common cause of pericarditis is “idiopathic”, likely due to infection with a virus. Of the known viruses, Coxsackie and echoviruses lead the list, but many others such as adenovirus or mononucleosis are possible. Non-viral causes include spirochetes - syphilis and borrelia (lyme); and the “atypicals”, Chlamydia and mycoplasma.

HIV infection both makes TB more likely and adds to the spectrum of other possibilities: lymphoma, Kaposi’s sarcoma, Cryptococcus, Nocardia, HSV, CMV, MAI, and Staph have all been reported to cause pericarditis in HIV+ patients.

8. How does this patient’s clinical presentation influence your assessment of the likely etiology of Process X?
   a. What are the most powerful “positive” symptoms/signs that support your lead diagnosis?
   b. The absence of which symptoms and signs auger against your lead diagnosis and how strongly?

a) The patient’s weight loss and dry cough strongly suggest TB, as do the findings of pleural effusion on P.E.

Furthermore, there are no suggestive symptoms or signs sepsis, uremia, autoimmune disease, or cancer – with the exception of lymphoma (see below).

The patient’s lymphadenopathy is relevant in 2 ways:
   1) It suggests another possible etiology, i.e. lymphoma, probably HIV-related;
   2) if TB is the etiology, it increases the likelihood that the patient is also HIV(+) most TB pericarditis in non-HIV-infected patients occurs alone, as only pericarditis, with associated pulmonary TB being the most common co-morbidity; however, of the reported cases of HIV-associated TB pericarditis, lymphadenopathy as a manifestation of disseminated TB has been seen in 40-80%.

In most series of TB pericarditis from Africa, the majority of patients (up to 90%) are co-infected with HIV. HIV co-infected patients have been reported to have cough in 95%, sputum in 75%, dyspnea on exertion (90%), and are more likely to have lost weight.
b. Although the lack of fever or sweats by history slightly diminish the likelihood of TB, over 25% of patients with TB pericarditis don’t report fever.

9. a) How is an etiologically definitive diagnosis of Process X made?

A definitive diagnosis is only made through isolation of AFB from the pericardium by microscopy or culture. However, less than 10% of smears of pericardial fluid or biopsy specimens reveal AFB, and culture for TB is positive in only about 50%. Thus, particularly in Africa, definitive diagnosis is rare before therapy must be initiated.

However, in the right epidemiologic setting i.e. in areas with high TB prevalence, empiric therapy for TB in patients with pericarditis is justified and response to therapy is considered a “definitive” diagnostic test.

b) What tests can be done to support the etiologic diagnosis (called “Disease X”)?

The EKG in TB pericarditis usually shows non-specific T-wave changes. Diffuse low voltage (<5mm limb, <10mm precordial) is seen in about 20-35%, and fewer have the classic changes of concave upward ST elevation and PR depression (~10%); electrical alternans is even less common.

However, tamponade is very unlikely if micro-voltage is not seen on the EKG.

Chest x-rays show an enlarged heart silhouette in >90% with TB effusion, an infiltrate consistent with TB in ~30%, and a pleural effusion in ~60%.

Sputum reveals AFB by smear or culture 10-55% of the time. Genexpert-PCR could be done on sputum given the frequent co-existence of tuberculous pneumonia. In smear (-) pulmonary TB it’s positive 60-70% of the time independent of HIV status.

10. a) What are the 3 stages of Disease X and how common is each stage?

TB pericarditis is thought to evolve through 3 “stages”:

- Effusive (a lymphocytic exudative effusion accumulates between the visceral and parietal pleura, drainage of which alleviates symptoms) … 80%
- Effusive-constrictive (the effusion takes on a porridge-like consistency, with the visceral pericardium adherent to and restricting the heart. Drainage of the effusion doesn’t relieve the presenting symptoms/signs of disease.) … 15%
- Constrictive (fibrosis of the pericardium restricts cardiac expansion, causing high pressures in both ventricles and signs of biventricular CHF, right >> left) … 5%

b) Which Physical Exam signs help differentiate the stages, and how accurate are they?

With a 16 fold higher prevalence of TB effusion (E) over TB constriction (C), very few findings associated with TB pericarditis make constriction more likely than effusion no matter how much more frequently they are found in patients with constriction (i.e. Bayes Theorem in operation!).
However, three findings may be an exception to this probabilistic assertion because they’re almost never seen in simple tuberculous effusions, although most modern-day examiners can’t identify them reliably: (Strang, Clin.Cardiol. 1984)
- Diastolic RV lift (~20% of patients with C)
- Early (close-to-S2), high-pitched/sharp “S3” at the left sternal border – the “pericardial knock” (45% of patients with C)
- Sudden S2 split on inspiration (~35% of patients with C)

Other findings strongly suggest C: (McGee)
- Kussmaul’s Sign: inspiratory increase in JVP, 50% with C, ~0% E (but also seen in severe CHF, pulmonary embolism, RV infarct, restrictive cardiomyopathy)
- “M” or “W” form of the JVP due to sharp X and Y descents (Y descent eliminated in E)

Some findings alter the probability of C relative to E, but none alone make C more likely than E:
- Edema (25% E, 95% C)
  - (N.B. although a patient with C is 4 times more likely to have edema than is a patient with E, because of the difference in prevalence of the 2 conditions, a patient with edema is still ~4 times more likely to have E than C… blame Bayes!)
  - Ascites (10-75% E, 75-90% C)
  - JVP >10 (15% E, 50% C)
  - Dullness to the right of the sternum (95% E, 25% C)
  - Friction rub (~20% E, 4% C)

Both E and C demonstrate the following signs with equivalent frequency: HR>100 (90%), palpable PMI (60%), diminished heart sounds (80%), pulsus paradoxus (25-30%).

N.B. Pulsus of >10 is seen in ~30% of patients with C, but none with C have pulsus >20; in tamponade due to effusion, 80% have pulsus >20.

11. What is the most dangerous early complication of Disease X, and how is it diagnosed at the bedside?

Cardiac tamponade, in which intra-pericardial pressure exceeds diastolic filling pressures and impairs cardiac output, is the feared complication of this disease occurring in ~10% of patients reported from South Africa.

In tamponade, elevated JVP is seen in 100% (unless complicated by hypovolemia), HR >100 in >90%, and pulsus paradoxus >12 in 98% (and usually between 20-50, with 80% having pulsus >20 and 40% >40); specificity of PP >12 for tamponade of those with effusions is ~85% (McGee). Of note, even with tamponade, a rub is frequently audible, and the BP >100 in >60%.

12. What is the late complication of Disease X, how frequently does it occur, and can it be prevented?

Constrictive pericarditis is the late complication of TB pericarditis, developing in ~5-20% of those with effusive pericarditis treated with a 4-drug anti-TB regimen. Although a Cochrane meta-analysis concluded that the scant evidence available was insufficient to recommend the addition of
steroids in patients with TB pericarditis, the evidence leans in favor of a month (to 3) of tapering high dose prednisone to improve mortality, obviate the need for (repeat) pericardiocentesis, and possibly decrease the likelihood of constriction developing.

13. Which other disease can be a major source of diagnostic confusion with the late complication of Disease X in East Africa/Uganda?

The principle source of diagnostic confusion with constrictive pericarditis in East Africa is the restrictive cardiomyopathy, endomyocardial fibrosis (EMF). Some studies report that EMF is the most common cause of CHF in Uganda.

Both diseases present with signs of right-sided heart failure, normal to moderately-enlarged hearts with subtle not-very-displaced PMIs without heaves, possibly Kussmaul’s sign and frequently a normal-sounding heart.

The fibrosing process in EMF often tethers the mitral or tricuspid valves causing regurgitation, and so murmurs of MR or TR in patients with CHF and non-dilated hearts suggest EMF. The findings noted in #10 above can help assess diagnostic probabilities, as can the EKG (diminished voltage in 30% with C; LAD supports a myocardial > pericardial process), or CXR (i.e. look for (rare) pericardial calcification in tubercular constriction, and signs of co-existing pulmonary TB).

14. What is the prognosis and treatment of the patient in the vignette?

Prior to TB antibiotics, TB pericarditis was fatal 80-90% of the time. Currently a 4-drug regimen for 6 months results in about a 10-25% mortality, and some data suggest lower rate of progression to constriction when steroids are used (NEJM, 2014).

Mortality in HIV+ patients reach 40% if HIV-HAART treatment is delayed.

Suggested Readings:

Mayosis BM, et al Tuberculous Pericarditis Circulation 2005;112;3608-3616

Maher D, Harries AD Tuberculous Pericardial effusion: a prospective clinical study in a low-resource setting-Blantyre, Malawi IntJTubercLungDis 1997 1(4):358


Syed FF, Mayosi BM A Modern Approach to Tuberculous Pericarditis Progress in Cardiovascular Diseases, Vol. 50, No. 3 (November/December), 2007: pp 218-236


Hakim JG Double blind randomised placebo-controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients Heart 2000; 84:183–188

Wragg A., Tuberculous pericarditis and HIV infection Heart 2000;84:127–128

Constant, J. Bedside Cardiology 4th Ed. Little, Brown 1993