Introduction:

Welcome to CUGH's bi-weekly 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 Jillian Morgan at jmorgan@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 29 – BREATHLESS AND PREGANT

A 22 year old woman, married for 2 years and pregnant 7 months with her first child, began experiencing significant dyspnea on exertion about 2 months ago. Since then her dyspnea progressed such that recently she's had to sleep leaning against the wall. Over the past week she's awoken nightly with dyspnea relieved only by sitting bolt upright for ~15-20 minutes, her ankles have become swollen, and now she gets breathless simply walking around her one room house. She has felt "hot" intermittently, and sometimes coughs with clear sputum that's occasionally blood-streaked.

She remembers no lengthy illnesses as a child, but did lag behind her teen-age friends when running and she fatigued more easily e.g. stopping to rest when walking over the hills to the Kisoro market from her village. She remembers when she was younger bouts of coughing up "pure blood" after exertion, but not for the last few years. She's had pneumonia once about 2 years ago, treated with antibiotics, and is HIV negative. She has felt her heart "racing" for 10-30 minutes on many occasions, often beginning suddenly at rest, but never sought medical attention for it. Twice, when the heart racing was prolonged for more than a half hour, she was very short of breath - which dissipated when her heart slowed abruptly. She's had no weight loss or night sweats.

Physical Exam: A young slight woman sitting upright breathing rapidly, surrounded by mother, father, husband.

BP 90/50; HR 120 regular, with premature contractions; R 36; T 99 oral

mouth: no thrush, normal dentition, no petechiae; conjunctiva normal without pallor;

neck: JVP: ↑ 12 cm above angle sitting up; + HJR (>4 cm, maintained for 10 seconds); Θ Kussmaul sign; thyroid palpable, soft, normal size/texture without bruit

lungs: good air movement, rales bilaterally half way up lung fields; no wheezes heard;

heart: forceful RV lift, parasternal; systolic retraction in 5th ICS, MCL, preceded by impulse in 3rd ICS, MCL

↑↑'d S_1; loud P2 heard best inspiration;

"triple sound" around S_2 at apex, best heard with diaphragm

Gr 1-2/6 holosystolic murmur, medium-pitched, at apex → radiating to axilla

Gr 2/6 mid-systolic, crescendo-decresendo murmur upper left sternal border, no radiation

abdomen: distended normal, 7 month gestation; no hepato-splenomegaly or ascites;

extremities: +1-2 edema to mid-shin bilaterally, with no difference in calf circumferences.

1. **What is the frame of this case (i.e. the key clinical features the final diagnosis must be consistent with) from the <u>history</u>?**

   - *22 year old woman*
   - *pregnant 7 months*
   - *2 months of progressive SOB, now with orthopnea and paroxysmal nocturnal dyspnea*
   - *> 10 year past history of fatigue, hemoptysis, and palpitations*

2. **Dysfunction of which organs (or systems) are potential causes of shortness of breath in pregnant women, especially in Africa? Explain.**
   Which is most likely in this patient and why?

- *Anemia: A major contributor to premature delivery and maternal mortality in the rural tropics, anemia during pregnancy is often multi-factorial: iron-deficiency due to menses, multi-parity without pre-natal vitamin supplementation, and/or endemic hookworm infection; malaria induced hemolysis, hypersplenism, and/or the anemia of chronic inflammation; other infections such as HIV, schistosomiasis, etc.*

  Pregnancy causes a further drop in hemoglobin/hematocrit, and increases tissue oxygen demand and cardiac output. Dyspnea on exertion and fatigue are common as hemoglobin falls below 8 mg/dl. However, anemia uncomplicated by heart failure will <u>not</u> cause sudden bouts of palpitations, orthopnea or PND; and anemia as the cause of dyspnea leaves unexplained the long history of hemoptysis in this patient.

- *Lung disease: Asthma, a common disorder under-diagnosed in Africa, could explain the exertional dyspnea (i.e. exertion-induced bronchospasm) and even the episodes of nocturnal dyspnea and inability to lie flat. During asthma attacks, people prefer to sit up to have gravity assist with diaphragmatic excursion, and paroxysms of bronchospasm can be provoked by pregnancy-induced gastro-esophageal reflux disease, GERD. Additionally, lifelong untreated asthma is a common underlying cause of bronchiectasis, which could explain the patient's intermittent hemoptysis, although bronchiectasis is almost always accompanied by a history of copious sputum production too.*

  The most common cause of hemoptysis is bronchitis, acute or chronic, but it would be unusual for bronchitis to cause frank blood without sputum (as in the past history our patient provided), and wouldn't help explain her progressive dyspnea over the past 2 months - i.e. not a very "parsimonious" diagnosis.

  Tuberculosis rarely causes significant shortness of breath until end-stage, or when complicated by massive pleural effusions which weigh down the diaphragm. Furthermore, in this patient there's no history of weight loss or night sweats, and the hemoptysis of many years is not consistent with active TB.

  In Africa a pulmonary complication of HIV must always be considered in a young woman with dyspnea, but our patient gives a history of being HIV negative, and has no constitutional symptoms to increase a low suspicion of an HIV-related pneumonia like PCP.

  Pregnancy is a hyper-coagulable state and progressive dyspnea, cough and hemoptysis should trigger a consideration of multiple pulmonary emboli. However multiple PEs would not explain the orthopnea or PND, nor the longer

history of symptoms; and the patient has none of the risk factors for DVT in pregnancy (AIM 2009: 151:85-92): symptoms in the left leg, calf circumference difference of >2 cm, and first trimester presentation (though presentations are more likely to be later in Africa).

- *Cardiac:* ***Congestive heart failure*** *(CHF) is the organ/system-specific diagnosis suggested by the history. Progressive dyspnea on exertion for 2 months followed by orthopnea and PND is classic for the evolution of left-sided CHF, and the prior history of easy fatigue (importantly, corroborated by specific examples) for many years suggests an insidious process. The marked worsening of old symptoms and the appearance of new ones during the patient's first pregnancy is likely to be more than coincidental.*

3. **How could pregnancy be potentially related to new-onset heart failure? Explain.**

Pregnancy could be relevant to new-onset CHF in 2 ways: a) as a direct cause of "primary" myocardial dysfunction through a hormonally-mediated toxic effect on heart muscle, or by precipitating CHF in patients with preexisting cardiac disease through the hemodynamic stress of pregnancy.

The first mechanism underlies "peri-partum cardiomyopathy", a dilated cardiomyopathy occurring between 1 month before and 5 months after delivery. However data suggest that this interval may be too narrow, and probably the same (unknown) "toxic" mechanism is responsible for the systolic dysfunction seen in some patients on both ends of the arbitrarily-defined 6 month time frame.

Pregnancy can transform previously silent cardiac dysfunction from any etiology into overt heart failure through the normal hemodynamics that accompanies it: an average 50% increase in blood volume which peaks at around 6 months gestation, and an expected increase in heart rate of 10-20 beats/minute. To accommodate these physiologic changes, an increase in stroke volume and a decrease in systemic vascular resistance occur normally, but if the heart can't tolerate the increased work load without increasing LV pressures, symptoms of CHF will ensue. With labor, cardiac output and blood pressure both increase and after delivery the vena cava is decompressed when uterine blood suddenly enters the circulation, increasing cardiac filling pressures acutely.

4. **What are the top 4-5 diagnostic considerations for new-onset CHF in a young woman in Uganda?**

- *Rheumatic heart disease: RHD is more than 100 times more prevalent in the 3rd world than in the West. Mitral disease, particularly mitral stenosis, commonly becomes overtly symptomatic for the first time during pregnancy.*

- *Congenital heart disease: Because it's not diagnosed during childhood in rural Africa, congenital disease (that rarely reaches adulthood undiagnosed in the West) often presents for the first time during pregnancy in Africa. Although most congenital heart disease is tolerated well during early adulthood and pregnancy, severe cases of congenital aortic stenosis, VSD and Eisenmenger Syndrome, Ebstein anomaly (displacement of TC valve, small RV, often ASD), Tetralogy of Fallot, Coarctation of the aorta, patent ductus arteriosus, etc. can decompensate with the normal hemodynamic alterations of pregnancy.*

- *endomyocardial fibrosis (EMF): The most common restrictive cardiomyopathy in the world, EMF is most common in Africa, and first described in Southwest Uganda. According to some reports, EMF is the leading cause of heart failure in Uganda and usually presents in childhood or early adulthood. Thus, it's a major consideration in this patient.*

- *dilated cardiomyopathy/myocarditis (DCM): Dilated cardiomyopathy is a very common cause of heart failure in Africa, diagnosed in 20-50% of hospitalized patients with CHF. Causes range from infection/myocarditis (from HIV, other viruses, trypanosomiais, etc.), immunologic responses to infection, nutrition (beri-beri), toxic (alcohol), genetic and "idiopathic".*

- *peri-partum cardiomyopathy (PPCM): PPCM is one of the causes of dilated cardiomyopathy that's much more prevalent in Africa, and of particular consideration in this pregnant patient despite her falling outside the window of the timing criteria: 1 month pre to 5 months post-partum (see #3 above).*

5. **Of these which are *almost* ruled out by the "timing" features of the history?**

Both EMF and DCM usually progress more rapidly than the ~10 years of fatigue/dyspnea symptoms suggested here. However, particularly in remote areas like rural Uganda without easy access to healthcare, long-term symptoms can actually have different etiologies over time, e.g. severe anemia secondary to hookworm, malaria, etc. can cause a vague history of dyspnea, which is later compounded by a more recent problem like cardiomyopathy.

EMF usually follows a relentlessly downhill course over 2-6 years, but a 10 year history is possible.

As mentioned above, PPCM is defined within a 6 month period starting 3 months after symptoms actually began in this patient (but as above, "variant PPCM" could still be possible).

6. **What is the significance of the Physical Exam in this patient? Explain the significance of the most important 6-10 findings on exam (both positive and negative findings).**

- *JVP, HJR, edema: suggest increased right ventricular pressures. (N.B late in pregnancy, some increase in JVP is normal due to increased blood volume, and edema is common from both the increased volume and the gravid uterus compressing the vena cava.) The degree of JVP elevation combined with the sustained HJR for more than 10 seconds are abnormal.*

- *Bilateral rales, no wheezing: strongly suggest bilateral alveolar fluid, either a transudate (as in heart failure) or an exudate (as in infection). In this symptom context, CHF is far more likely. Absence of wheezing and presence of rales while dyspneic rules out asthma.*

- *RV lift: suggests a hypertrophied right ventricle that's adapted to chronically elevated pulmonary artery pressure; thrusting and forceful, it's quite opposite the weak RV lift from an RV dilated by primary cardiac muscle disease. (N.B. an RV lift can be seen in thin pregnant women in the later trimesters due to increased blood volume.)*

- *Systolic retraction, preceded by an impulse in the 3rd ICS, MCL: A systolic retraction (where the PMI is expected) indicates an enlarged RV dominates systole, sucking in the intercostal muscles overlying the contracting left ventricle as it's pulled posteriorly behind the RV. It suggests that the left ventricle is not enlarged despite symptoms of left-sided heart failure and crackles. (Though not seen in this patient, hypertrophied right ventricles can cause such clockwise rotation of the heart that a forceful left-sided "PMI" is actually the leftward-displaced RV impulse.)*
  The preceding impulse in the 3rd ICS is likely to be the left atrial impulse, suggesting left atrial hypertrophy/enlargement.

- *Murmurs: There are 2 systolic murmurs heard in this patient, differentiated by their duration, pattern and radiation… but not pitch. (Pitch can be misleading due to the Gallavardin phenomenon in which lower-pitch elements of a murmur, which have less energy, attenuate with distance. The same murmur can thus sound progressively high-pitched further from its source.) In this patient, there's a left sternal border systolic murmur, crescendo-decrescendo without radiation: this short, mid-systolic murmur is the normal aortic flow-murmur of pregnancy from increased blood and stroke volume. There's also a Gr 1-2/6 medium-pitched, holosystolic (or "blowing") murmur radiating to the axilla. This is due to mitral regurgitation. The duration is holosystolic because the pressure difference and blood flow spans the entire systole. According to traditional teaching it radiates in the direction of flow - to the axilla - but this explanation is probably incorrect: according to more recent thinking (based on tracing the actual direction of blood flow in MR medially and posteriorly, not up and out) the radiating sound is carried along the ribs – and thus to the axilla.*

  Murmur pitch is produced by the velocity of turbulent blood flow across an orifice, which in turn is determined by the difference in pressure between the chambers on either side. In MR, the chambers are the LV and the LA in systole: a large gradient in pressure implies a low LA pressure and hemodynamically <u>insignificant</u> flow - and produces a high pitch murmur; a medium pitched murmur means less difference in pressure between the chambers either due to higher LA pressure (from chronic CHF or mitral

stenois) or a left ventricle failing to contract forcefully. A low-pitch MR murmur usually means more MR and greater hemodynamic severity… " the more the flow, the more the low".

The MR in this patient however is likely to be hemo-dynamically insignificant: the LV PMI is non-palpable/non-displaced, supporting the possibility of raised LA pressure (and thus a medium pitch MR murmur) unrelated to ventricular failure.

- *↑↑'d S_1: a loud S1 is due to the wide separation of the mitral (and/or tricuspid) valve leaflets at start of systole and the leaflets "slamming shut" at high velocity when the valve closes. A loud S1 is thus heard in tachycardia, short PR interval, and mitral stenosis (MS). In MS, the scarred valves don't float back towards the mitral orifice in late diastole, are maximally separated when the ventricle begins to contract, and come together at their maximal closing velocity. <u>Often the only clue to underlying MS, a difficult murmur to hear, is a sharp, loud S1.</u>*

- *"triple sound" around S_2 at apex: This is very revealing. The first component heard is the A_2, normally heard at the apex; the second is the P2, which is usually <u>not</u> heard at the apex but is when the pulmonary artery pressures are high. N.B. The loud P2 at the base is consistent with this apex finding, and both suggest pulmonary hypertension); the third sound is the "opening snap" of a thickened but still-mobile mitral valve.*

7. **What was missed on PE?**
   What physiologic implications of *other* signs found on exam lead you to that conclusion?

   Why was the key diagnostic finding missed?

- *The diastolic murmur of <u>Mitral Stenosis</u> was missed on exam.*

- *Physiology of the PE that leads to the suspicion of MS: The elevated RV pressure (JVP, HJR) is chronic, accompanied by a strong lift of RV hypertrophy. The loud P2 heard at the apex suggests pulmonary artery hypertension. The left-sided heart failure symptoms and signs (rales) are not caused by disease in the left ventricle, but by obstruction to flow into the left*

ventricle, i.e. mitral stenosis. Although the loud S1 in this patient could be caused by either tachycardia or mitral stenosis, the triple sound/opening snap at the apex indicates mitral stenosis.

- *The murmur of MS was missed on PE for many reasons:*
  - it's very hard to hear: the murmur is a low pitch "rumble" often only heard with the bell within 1 cm of apex with the patient in the left lateral decubitus position. You have to search for it and listen carefully.

  - With tachycardia found in this patient (secondary to the catecholamines released in decompensated CHF), there is decreased diastolic filling time and the murmur can become inaudible. A loud S1, particularly if the patient is not tachycardic, is often the only clue to "silent MS" in the appropriate clinical setting.

  - Studies on the PE have shown that physicians often miss diastolic murmurs and tune into systolic murmurs more readily. MS is rare now in the West: most young physicians have never heard the murmur before.

8. What did the EKG and CXR show?

- *EKG: Left atrial enlargement (LAE) with wide biphasic P waves and right atrial enlargement; right ventricular hypertrophy (RVH) with R > S in V1-2, no LV hypertrophy, clockwise rotation, axis vertical/rightward shift.*
- *CXR: enlarged left atrium with straightening of left heart border, normal size heart, elevated and horizontal left bronchus; prominent PA and right heart border, central alveolar edema and cephalization of flow;*

9. How would you treat this patient?

- *An important focus of treatment in MS is slowing the heart rate - to allow more time in diastole to empty the atrium, fill the ventricle and improve cardiac output. MS is one of the rare situations in which acutely decompensated CHF is treated with beta-blockers. If the patient were in atrial fibrillation, digoxin, also well-tolerated in pregnancy, could be used.*

- *After the heart rate slows and cardiac output increases, a diuretic should be given to relieve pulmonary congestion and symptoms of CHF.*

- *Particularly if there were indications of hypoxia, if oxygen were available it should be given to protect both mother and fetus.*

- *Since fluid in the alveoli is fertile soil for infection and neither the PE nor CXR can reliably rule out pneumonia complicating CHF, an antibiotic with coverage for community-acquired pneumonia is probably appropriate for a few days in this critical situation.*

10. **What is the relevance of Uganda or Africa in this patient's presentation?**

Rheumatic heart disease (RHD) is rampant in Africa and the developing world - which hasn't seen the dramatic decrease in the incidence of the disease observed in the West where RHD is now rare. The difference in the incidence of RHD between the two worlds is multifactorial including changes in pathogenicity of strains of the b-hemolytic streptococcus, living conditions, access to care, nutrition, etc.

Most RHD is silent: In Africa and Asia, clinical exam detects RHD in 2-3 school-aged children per 1000, while echocardiography detects RHD in 2-3% of school children (!), about a 10 times increase (NEJM 357:470, 07). Most RHD affects the mitral valve, and mitral stenosis often presents to medical attention for the first time in pregnancy due to the hemodynamic stress of normal pregnancy.

As noted in #4 above, other causes of heart disease are far more common in Africa than in the West as well, including EMF, DCM and PPCM.

Suggested Readings:

Silwa, K., et al. Epidemiology and Etiology of Cardiomyopathy in Africa *Circulation.* 2005;112:3577-3583

Essop, M.R., et. al, Rheumatic and Nonrheumatic Valvular Heart Disease: Epidemiology, Management, and Prevention in Africa Circulation. 2005;112:3584-3591

Chandrashekhar, Y. et. al, Mitral stenosis Lancet 2009; 374: 1271–83

Marijon, E., et. al Prevalence of Rheumatic Heart Disease Detected by Echocardiographic Screening N Engl J Med 2007;357:470-6.

Carapetis, J.P. Rheumatic Heart Disease in Developing Countries NEJM 2007, 357;5

Reinold, S.C., et. al. Valvular Heart Disease in Pregnancy N Engl J Med 2003;349:52-9.

Constant, J. *Bedside Cardiology* 4TH Ed. Little, Brown and Co. 1993