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 34 – SEVERE HYPERTENSIVE WITH DYSPNEA

A 72 year old woman with a history of hypertension presents to the Chronic Care Clinic of Kisoro District Hospital for a scheduled visit but also complaining of difficulty breathing for some weeks.

Hypertension was diagnosed a few years ago by her Village Health Worker while screening blood pressure during a home-visit, and since then she has been followed in the Chronic Care Clinic. She was started on a thiazide diuretic for a systolic BP >190 and soon thereafter propranolol and nifedipine were added for difficult-to-control hypertension. Over the past 2 years, her blood pressures have ranged 170-200/100-110 with good adherence by report, and with reliable clinic follow-up documented.

Now she complains of feeling increasingly short of breath for the past few weeks, a complaint she never voiced before. With probing however, it's apparent that she's had increasing dyspnea on exertion for the past 3 years, first noticed when climbing hills to dig in her fields, and over the past year even on walking ~25 meters up gradual inclines. For the past year she has had to sleep partially sitting up, reclining to only about 45 degrees because of breathlessness when lying flat. She's gradually lost weight, hasn't had leg swelling, or dyspnea that suddenly wakes her from sleep. She's had a cough, particularly at night, dry without sputum, but no fevers or sweats. She hasn't audibly wheezed nor did she have problems (as did some of her siblings) with shortness of breath when younger. She never smoked.

Physical Exam: Pleasant elderly woman sitting upright in no distress

BP: 172/107, repeated x 2; HR 78; RR 22 unlabored; T: 98.2; pulse oximetry: 84% (repeated with 2 oximeters)
Conjunctiva: no pallor or petechiae;
Fundi: no papilledema; scattered hard exudates; no soft exudates or hemorrhages; A/V~1/3 with generalized narrowing, tortuosity and A/V nicking noted;
Neck: thyroid normal; no lymphadenopathy; no JVP; no HJR;
Chest: increased AP diameter [AP to lateral diameter ~1] with prominent sternum and slight dorsal kyphosis; trachea midline
Lungs: hyper-resonant to percussion bilaterally particularly right upper anterior chest;
decreased breath sounds diffusely, with intermittent faint high-pitched long expiratory wheeze audible;
early inspiratory crackle(s) heard at bases bilaterally (~1-3 per second when heard);
Heart: prominent epigastric impulse; no PMI nor lifts/heaves palpable;
cardiac percussion: dullness ~8.5-9 cm from mid-sternum;
S4 audible in left lateral decubitus; S1, S2 narrowly split with increased P2; no S3;

Abdomen: no bruits; no hepatosplenomegaly, masses, distention, guarding or tenderness;
Extremities: without edema or clubbing; pulses +2 throughout
Neurologic: grossly normal mental status, Cranial Nerves, motor, sensory, gait, cerebellum; reflexes +2

1. What is the "frame" of this case from the patient's history (i.e. the *key* clinical features the final diagnosis must be consistent with and/or explain)? Explain the clinical relevance of each.

- *elderly woman with significant hypertension picked up during asymptomatic screening, now presenting for a scheduled appointment*
- *dyspnea for 3 years, progressive, worse recently with a dry cough at night*
- *lying flat induces shortness of breath; she has to sleep at a 45 degree angle but has no paroxysms of nocturnal dyspnea or leg swelling*
- *weight loss but no fever or other constitutional symptoms; never smoked*

- elderly woman with significant hypertension picked up during asymptomatic screening, now presenting for a scheduled appointment

[The "iatrotropic stimulus" or reason the patient comes to medical attention, is highly correlated with the likelihood of some acute pathology causing the complaint. In this patient this theme is relevant twice: first, her hypertension was discovered during screening while she was asymptomatic. It's therefore less likely to be associated with symptoms in the near future than if it was diagnosed for the first time during a symptomatic bout of cardiovascular disease as is so often is in rural Africa; second, she's complaining of shortness of breath during a routinely scheduled clinic visit for other problems (BP check). The dyspnea is thus more likely to be caused by an indolent disease unaccompanied by the florid signs that facilitate diagnosis than is dyspnea in the patient who comes to the clinic short of breath.]

- dyspnea for 3 years, progressive, worse recently with a dry cough at night

[Different causes of dyspnea have their own natural history untreated, which, despite broad overlap between them can be very helpful in diagnosing the primary problem (discussed below).]

- lying flat induces shortness of breath; she has to sleep at a 45 degree angle but has no paroxysms of nocturnal dyspnea or leg swelling.

[The lack of either edema or PND despite long standing inability to sleep flat suggests that the apparent "orthopnea" isn't cardiac, i.e. is NOT due to increased fluid volume and high intra-cardiac pressures that make the lung boggy, heavy and restricted – and worse when supine. (N.B. This is a good example of why it's prudent to avoid using "medicalese" to describe symptoms in the primary clinical database (write-up and presentation) since medical terms often infer more specificity than is warranted from the history and narrow the scope of diagnostic considerations. For example in this case, if "breathlessness when lying flat" was called "orthopnea", and if the term "orthopnea" implies "heart failure" to some readers/listeners, it could be inadvertently misleading and close off consideration of other causes of the complaint e.g. obesity or obstructive lung disease in which diaphragmatic descent is easier when sitting upright. N.B. There is less risk of ambiguity when medical terms are used in the "negative", e.g. "no PND or edema…")]

- weight loss but no fever or other constitutional symptoms; never smoked

[Smoking is a major cause of lung disease and dyspnea worldwide thus its absence here is notable. Heart failure, a prominent cause of dyspnea in severe hypertensives like our patient, is associated with weight gain from edema. Sometimes however, due to cytokines, catecholamines and the hypercatabolism associated with end-stage heart failure, patients note the loss of lean body mass and complain of "weight loss". However this end-stage state is almost always associated with significant edema and other florid signs of heart failure, absent here. Tuberculosis is a common cause of pulmonary symptoms but active TB is an infrequent cause of dyspnea unless it's complicated by pleural effusion, significant atelectasis, pneumothorax or pericardial disease. Other constitutional symptoms accompany the weight loss of TB – fever, sweats, etc – which weren't present in this patient.]

2. What are the most important findings on physical exam, both "positive" and "negative", and what do they tell you?
What exercise maneuver/measure would be diagnostically informative?

- BP: 172/107*: significant hypertension despite 3 medications is designated "resistant hypertension" and raises the possibility of secondary causes such as renal artery stenosis, hyperaldosteronism, chronic renal insufficiency, etc. - although severe <u>essential</u> HT is still the most common. (In African (or African-American) populations, resistant HT is even less likely than in whites to be due to a secondary cause than to genetic "essential hypertension".)*
The absence of a renal bruit diminishes the probability of renal artery stenosis.
The funduscopic changes suggest hypertension that's chronic, and the absence of any renal bruit diminishes the probability of renal artery stenosis modestly (LR negative of 0.6 and a sensitivity of ~30-60%, it decreases the probability by about 10-15% from its (low) pretest probability).

- Pulse oximetry, 84%, in no distress*: In the context of the patient's apparent comfort, the pulse ox of 84% is perhaps the most important finding. It suggests a chronic process, and in the absence of an overt cardiac shunt with murmurs and/or heaves, points to the lungs and long-standing compensated pulmonary disease as the source of the dyspnea.*

- increased AP diameter [AP to lateral diameter ~1] with a prominent sternum and slight dorsal kyphosis: *this is a description of a "barrel chest". Normally the AP diameter is .70 the lateral diameter, increasing with age, with an upper limit of normal 0.90. Although "false positives" are seen in the elderly, in a patient with dyspnea and hypoxemia a barrel chest is a sign of obstructive lung disease, usually severe.*

- hyper-resonant to percussion bilaterally particularly right upper anterior chest: *hyper-resonance, particularly in the right upper anterior chest, suggests COPD with a LR (+) of 5.*

- early inspiratory crackle(s) heard at bases bilaterally (~1-3/second when heard); *Crackles are heard in many types of lung disease and in heart failure, and can be described by their timing - early (heard only in first half of inspiration) or late (persisting to the end of inspiration), and frequency. Crackles of COPD are early and few (1-4) whereas those of interstitial fibrosis are late and frequent (6-14); pneumonia and CHF produce crackles*

between these extremes. The presence of early inspiratory crackles suggests COPD (LR 14.6) and severe obstruction at that (LR 20.8).

- faint high-pitched long wheeze: *suggests obstruction (LR(+) 2.8; LR(-) 0.8; sensitivity 13-56; specificity 86-99). The long duration and high pitch suggest severe obstruction; the amplitude doesn't reflect severity one way or the other.*

- no JVP, edema, RV lift or hepatomegaly: *no signs of RV failure in this patient. (RV failure could have been caused either by LV failure or cor pulmonale.)*

- prominent epigastric impulse; S2 narrowly split with increased P2; no PMI nor lifts/heaves palpable;

The prominent epigastric impulse is caused by an enlarged and/or hypertrophied RV which isn't causing an RV lift due to the barrel chest; the P2 is loud due to pulmonary hypertension, but the narrowly split S2 suggests that the PHT is not yet causing the RV to fail and delay contraction, which would widen the split S2.

The <u>active exam maneuver</u> that should be done to support the diagnosis of emphysema is exercise pulse oximetry: in a patient with significant COPD-emphysema the O2 saturation should drop even more with exercise due to increased blood velocity across the remaining alveoli which compromises gas exchange by limiting the time for O2 diffusion. The increased "shunting" of de-saturated blood through the alveoli drops the O2 saturation.
[N.B. In this patient, walking 25 meters at a rapid pace dropped the O2 saturation from 84 to 70%.]

3. *Which organ* affected by *what disease process* is causing the patient's dyspnea? What supports your diagnostic impression?

The patient's dyspnea is due to lung disease, and the pathophysiology is that of <u>chronic obstructive pulmonary disease (COPD)</u>.
Given the patient's severe hypertension, dyspnea on exertion, orthopnea and no smoking, the initial consideration might be CHF. However, pulse oximetry of 84% (pO2 in the 50's) without any respiratory distress could only be caused by lung disease in the absence of a large cardiac shunt. In heart failure, hypoxemia results from fluid acutely transudating into the interstitium and alveoli (i.e. pulmonary edema) faster than the enhanced lymphatic network, working overtime, can compensate and drain it. Crackles would be heard throughout the lungs and the patient would be in severe distress.

The dyspnea in this patient with severe HT picked up on asymptomatic screening a few years earlier, is due to COPD. The physical exam, as analyzed above, strongly and consistently suggests obstruction (the "composite LR+" of all the signs together is >200).

4. What is the dominant risk factor for this disease worldwide, and what proportion of total cases of the disease does it explain?

What are the principle causes of this disease in Africa and the developing world?

Smoking is the dominant risk factor for COPD worldwide. With COPD defined as FEV1/VC <70% or chronic cough/phlegm/wheeze, smoking is responsible for 45-75% of cases of COPD worldwide. This means that 25-55% of cases of COPD worldwide are NOT related to smoking, data that seem surprising to Western physicians. The prevalence of COPD in non-smokers in the NHANES III study in the U.S. was 7%. In less developed countries it's higher.

From a review by Salvi and Barnes:

"Findings from the Swedish OLIN and US NHANES III studies reported that the population-attributable risk of COPD from smoking was 45% and 44%, respectively, indicating that more than half of COPD cases were due to nonsmoking causes. In the BOLD study of the prevalence of COPD in 12 countries (Australia, Austria, Canada, China, Germany, Iceland, Norway, Philippines, Poland, South Africa, Turkey, USA), Buist and colleagues reported a very high prevalence of COPD in never-smokers. Up to half of COPD cases are due to non-smoking causes…"

The principle causes of COPD in sub-Saharan Africa and other regions yet too poor to have a large population of heavy smokers include: (see Salvi/Barnes)

- <u>Biomass fuel exposure indoors</u>: biomass fuel – firewood, dried dung, agricultural mass residues - is the main fuel for heating and cooking for 3 billion people, or half the world's population. 50% of the deaths from COPD in the developing world are biomass induced, 75% of them women.

- <u>Tuberculosis</u>: the prevalence of COPD in patients with a history of TB varies from ~30% to 70%, increasing with the extent of prior disease and the duration since treatment completion. In studies in South Africa, TB was the strongest predictor of COPD with odds ratios for men and women of 4.9 and 6.6 for those with a history of TB. Studies in South America reveal the same, with TB history a stronger predictor of COPD than smoking or biomass exposure. In a large population study in 5 Latin American cities, the prevalence of COPD was 31% for patients with a history of TB vs. 14% for those without.

- <u>HIV</u>: HIV infection is a risk factor for emphysema, increasing the susceptibility of the lung to smoke-related damage and associated with inflammation, PCP colonization, endothelial injury and apoptosis, all of which lead to a significantly increased incidence of COPD in HIV-infected individuals.

- <u>Asthma</u>: "According to findings from a US-based study that followed-up 3099 patients for 20 years, those with active asthma were 10 times more likely to develop symptoms of chronic bronchitis and 17 times more likely to be diagnosed with emphysema than those without asthma, even after adjustment for confounding factors. Asthma was the strongest risk factor for subsequent COPD, more than even tobacco smoking (hazard ratio 12.5 vs 2. 9, attributable risk 18. 5% vs 6. 7%)." (From Salvi/Barnes)

- <u>Farming</u>: in rural areas in the U.S. COPD was diagnosed in 30% of farmers; about 8% of COPD overall is attributable to farming, tending livestock carries a 40% higher risk than agriculture and is correlated with concentrations of ammonia, hydrogen sulfide and dust exposure.

- <u>Poverty</u>: is a major independent risk factor for COPD, probably mediated through intrauterine growth retardation, poor nutrition (low intake of antioxidants) and housing conditions, childhood respiratory-tract infections, exposure to tobacco smoke, biomass smoke and other indoor air pollutants, and occupational risks.

The causes of COPD demonstrate an "epidemiologic transition": in impoverished rural regions of the world where people can't yet afford to smoke heavily, COPD is caused by biomass fuel, TB, asthma – in short, poverty. In the West, smoking cigarettes is dominates the causes of COPD. However emerging nations such as China, rapidly moving transitioning from diseases of poverty to diseases of development, are caught in an "epidemiologic trap": biomass and other causes of poverty-related COPD are still prevalent, but smoking is the bigger national risk: China has 30% of the world's smokers and 50% of non-smokers are exposed to tobacco smoke.

5. What is the likely root cause of the disease in this patient?
What additional history might substantiate your suspicion/hypothesis?

The cause of this patient's emphysema is lifelong exposure to biomass fuel. (She had no overt history of asthma, her chest x-ray showed no changes of old TB except for small calcified nodes, and an HIV test was negative.)

When asked open-endedly if there were any places where she noticed increased difficulty breathing, she immediately volunteered "the kitchen" - which she couldn't go into any more while food was being prepared on the open firewood stove.

Indoor air pollution from biomass produces over 75% of the world's exposure to particulate matter, and in far higher concentrations than seen in polluted cities. Biomass generates higher carbon monoxide, sulfur dioxide, nitrogen dioxide and small particulates. The burning of biomass generates mean concentrations of particulates 300-3000/mg/m^3: in the U.S. a public alert is sounded at 350, and an emergency is defined to be a concentration above 500.

Besides COPD, biomass exposure is associated with low birth weight offspring (30-40 gm lower), a 2-3x increase in childhood lower respiratory infections, impaired macrophage function and an increase in tuberculosis. In Guatemala, an association was found in women between biomass exposure and increased diastolic blood pressure, hypercoagulation and vasoconstriction.

6. What public health interventions are beneficial that Village Health Workers could promote and local families adopt to prevent the disease?

Biomass generates 95% of domestic energy in lower income countries. Because poverty in the developing world will be with us for decades, an improved biomass stove is the most cost-effective intervention for Sub-Saharan Africa.

Lower emissions may be achieved by modifying energy-use behaviors such as fuel drying, separating the kitchen from the house, using pot lids to conserve heat, elevating stoves to waist height to avoid bending over the fumes, building chimneys/fireplaces into the walls, attaching flues to stoves and maintaining stoves and chimneys, using charcoal more than wood or dung, heating water with solar, etc.

Suggested Readings:

McGee, Steven, *Evidence Based Physical Diagnosis* 2nd Edition, 2007, Saunders/Elsevier

Fullerton, D.G., et.al. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world Transactions of the Royal Society of Tropical Medicine and Hygiene (2008) 102, 843—851

Kurmi, O.P. et.al COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis Thorax 2010;65:221e228

Van Gemert, F, et.al The impact of asthma and COPD in sub-Saharan Africa *Prim Care Respir J* 2011; 20(3): 240-248

Salvi, S., Barnes, P. Chronic obstructive pulmonary disease in non-smokers *Lancet* 2009; 374: 733–43

Po, J.Y.T, et. al Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis Thorax 2011;66:232e239