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 35 – Platypnea with Sudden SOB

A 24 year old man, a farmer living in the Kisoro district with his wife and 2 children, presents with 10 days of increasing chest pain and shortness of breath.

He was previously healthy, able to work the fields every day, until 10 days ago when in Church on Sunday he experienced the sudden onset of mild right-sided chest pain that increased with inspiration. The next few days he was able to work but the pain progressed, precipitated by ever more shallow inspiration and accompanied by a dry cough. He started to feel "hot" and at night could sleep more comfortably lying on his right side. Over the next 3-4 days he was short of breath when walking to his field, and he stopped working 3 days ago. He took panadol (acetaminophen) with some relief of the pain, and coartem for the "hot" feeling, without relief. When the chest pain and cough worsened and he began feeling dyspneic when walking short distances around his house, he came to the hospital.

There was no one in his family who was sick recently, and he's never had this before. He's experienced no weight loss, but has had decreased appetite since getting sick. He's had no leg pain, or swelling in his legs or belly; feels less short of breath lying flat than sitting up; and doesn't wake from sleep short of breath as long as he lies on his right side. He doesn't drink, hasn't lost consciousness, and produces no sputum.

Physical Exam:
Well-developed, in no acute distress but breathing rapidly, talking in full sentences sitting up
BP: 110/75; HR 95; RR 30, shallow; T: 100.2 axillary

Skin: normal, no rashes
Eyes: no conjunctival icterus or petechiae; EOM, PERRLA;
Fundi: no hemorrhages, exudates; discs flat
Mouth: no thrush, no violaceous plaques;
Neck: shoddy lymphadenopathy, < 1cm; thyroid normal; no JVP/HJR
Trachea: slight deviation to the left at the supra-sternal notch
Chest: no point tenderness elicited over the ribs or intercostals muscles on the right; pain elicited with diffuse pressure over the right lateral rib cage
Lungs: left lung: clear to percussion and auscultation
right lung: dullness/flat to percussion half way up lung field;
bronchial breath sounds posteriorly mid-lung;
decreased breath sounds lower half, with absent vocal and tactile fremitus;
E-to-A egophony heard faintly lower lung, and more prominently mid-lung
No crackles;
Cardiac: PMI normal, not displaced; S1, S2 normal, no S3, S4; murmurs or rubs
Abdomen: no hepato-splenomegaly, masses, or tenderness
Extremities: normal, without clubbing or edema
Neurologic: normal mental status, cranial nerves, motor, sensory, cerebellar, reflexes

1. a) What is the "frame" of this case (i.e. the key clinical features the final diagnosis must be consistent with) from the *history*?
b) What is the clinical significance of each feature of the frame?

a) *The frame:*

- *sudden spontaneous onset of pleuritic chest pain, positional*
- *10 days duration; progressive*
- *absence of sputum*
- *dyspnea on exertion (DOE), progressive, without orthopnea or paroxysmal nocturnal dyspnea (PND) but with "platypnea"*
- *no constitutional symptoms of weight loss, etc. Normal health prior to 10 days*

b) *Corresponding clinical significance of each feature:*

- sudden spontaneous onset of pleuritic chest pain, positional
… suggests an inflammatory process involving surfaces that are stretched or rub together in inspiration (pleura/pericardium) or are involved in the mechanics of breathing (muscles, ribs). Location on the right augers against pericardial disease, and improvement when lying on the right suggests that splinting-limiting respiratory motion helps – as in right-sided intercostal muscle inflammation (rare, e.g. pleurodynia from Coxsackie viral infection) or pleuritis;
His young age and the history auger against rib fracture, pathological or traumatic;

- 10 days duration; progressive
… suggests an indolent process, less aggressive than a pyogenic pneumonia and too long-lasting and insidious for pulmonary embolism.

- absence of sputum
…. leans away from pneumonia with extension to the pleura, a very common cause of pleuritic pain with fever in Africa. Although pneumonias in the elderly often present without sputum, this would be distinctly rare in a healthy 24 year old - especially after 10 days of illness;

- dyspnea on exertion (DOE), progressive, without orthopnea or paroxysmal nocturnal dyspnea (PND) but with "platypnea"
… DOE, a sensation mediated by alveolar stretch receptors, suggests <u>diffuse</u> involvement of the lung parenchyma or interstitium (e.g. from fluid, inflammation, or widespread carcinomatosis) or impairment of the mechanics of breathing, as with large pleural effusions that weigh on the diaphragm.
In this patient CHF is unlikely given the pleuritic pain, the acuity of the presentation, and platypnea instead of orthopnea/PND. Platypnea, or the sensation of increased breathlessness when upright, is often associated with "ortho-deoxia" (or hypoxia when upright) and suggests more pathology at the bases of the lungs: gravity helps direct blood flow preferentially to the un-aerated segments of the lung increasing V/Q mismatch and hypoxemia - seen with pleural

effusions, PCP, etc. Effusions also inhibit diaphragmatic excursion and intercostal retraction.

- no constitutional symptoms of weight loss, etc. Normal health prior to 10 days …. Suggests that although the process may be indolent, there was no sign of it prior to 10 days ago i.e. this is a process that despite its sudden onset, progresses slowly.

2. What is the clinical significance of the findings on Physical Exam?

The increased respiratory rate if 30 shallow breaths per minute could be caused by either the pleuritic pain or by or by cardio-pulmonary processes. The low-grade fever suggests inflammation.

The absence of cardiac findings and the unilateral lung findings support the pulmonary origin of the DOE, consistent with the history.

The absence of point tenderness over the ribs and intercostals muscles steers thinking away from focal musculo-skeletal pathology. Tenderness with diffuse pressure is consistent with pleural pathology.

Deviation of the trachea to the left (in this clinical context) suggests either left lung atelectasis or fluid or air in the right pleural space pushing the trachea toward the opposite side.

Dullness to percussion half way up on the right suggests either an area of right base consolidation or pleural effusion, and the "flat" quality of the note leans toward effusion.

"Bronchial breath sounds" imply transmission of upper airway sounds – both high and low frequencies – to the surface of the lung. High frequencies are usually filtered out by normal lung, but are transmitted easily through consolidated tissue and preferentially through large pleural effusions - both of which are characterized by "bronchial breathing". Usually in consolidations, the bronchial sounds come through loud and clear, whereas in effusions they are diminished.

E-to-A "egophony" occurs when the few high frequency vibrations in EEEE are preferentially augmented in an effusion or consolidation and sound like AAHHH. Egophony in effusions is usually most prominent at the upper border of the effusion where lung tissue is compressed. (Compressed lung can also increase bronchial breath sounds above the effusion and be confused with a consolidation.)

Fremitus is caused by low-frequency sound vibrations and thus is diminished by effusions which block low frequencies, but is augmented by consolidation which readily transmits all frequencies.

Absence of crackles lessens the likelihood of parenchymal disease and consolidation, although they are sometimes absent in early pneumonias and can be present above effusions.

Thus the decreased fremitus in this patient suggests pleural effusion over consolidation, as does the diminished sound volume, the tracheal shift and the absence of crackles.
(N.B. Consolidation with an obstructed bronchus however can also cause diminished bronchial breathing and decreased fremitus. This may be impossible to distinguish from effusion on exam unless the trachea is shifted: away in effusion, and towards in obstruction (although tracheal shift is not a sensitive sign in either situation)).

3. a) What is the differential diagnosis and what's for and against each possibility in the differential?
b) How would HIV disease influence the differential?

a) The differential diagnosis is essentially that of pleural effusion in Africa, although given the limitations of the accuracy of the physical exam, it should encompass causes of pulmonary consolidation as well. In a previously healthy 24 year old who's been sick for 10 days, all etiologies of pulmonary consolidation also cause pleural effusion.

- *Parapneumonic effusion: pleural effusions occur in 30-50% of pneumonias and are usually sterile, caused by movement of inflammatory exudate into the pleural space from the lung. They are extremely common in Africa where community-acquired pneumonia is common, often complicates HIV or malnutrition, and is treated later (if at all) with antibiotics. The absence of sputum even after 10 days and the lack of acuity point against a community-acquired pneumonia from pneumococcus or other pyogenic organisms.*

- *Empyema: empyema is an infection of the pleural space by bacteria, usually with gross pus present. Often caused by more indolent anaerobic organisms from aspiration-induced pneumonias that go untreated, and more common in HIV infected patients, in this patient there are no known risks of aspiration such as alcoholism, epilepsy or other causes of loss of consciousness.*

- *Malignancy, solid tumor metastatic disease to the pleura: common as a cause of effusion in older populations with risk factors for cancer, in this patient his age, lack of constitutional symptoms and the time course of disease all make this diagnosis extremely unlikely.*

- *Tuberculosis (see below)*

- *Heart failure, cirrhosis, nephrosis: these systemic processes cause diffuse transudation across the capillary bed into the pulmonary interstitium and then the pleural space as per Starling's law: either via an intravascular increase in hydrostatic pressure (heart failure) or decrease in oncotic pressure (cirrhosis/nephrosis), and/or leakage of ascites through diaphragmatic pores (cirrhosis).*
  All are unlikely due to the lack of symptoms associated with these systemic diseases, the patient's chest pain, and his unilateral presentation of significant disease.

If the patient were HIV (+), 3 additional diagnoses should be considered, and 2 others mentioned above would be more common:

- *Kaposi's Sarcoma*
- *Non-Hodgkin's Lymphoma*
- *Pulmonary/pleural Cryptococcus*

More common in HIV (+) than HIV (-) patients are parapneumonic effusions and TB, which are by far the most common causes of effusions in HIV(+) patients; both cardiac and renal diseases are also more common in HIV (+) patients.

4. a) What's the most likely diagnosis?
b) Why is it most likely?
c) What is its pathogenesis and natural history?
d) What's the difference between its presentation in HIV (+) vs. HIV (-) patients?

a) Tuberculous pleural effusion is the most likely diagnosis in this patient.

b) It's most likely both epidemiologically and clinically. TB is the most common cause of significant pleural effusions in areas of Africa where the disease is endemic, and the pleura is the second most common site (after lymphadenopathy) of extrapulmonary TB, >20% of cases of extrapulmonary TB.

The clinical presentation fits well: Although mycobacterial disease is indolent clinically, TB pleurisy usually presents abruptly (65%). One third are ill for less than a week, and 2/3 are ill for less than a month before presenting to medical attention.

c) Most disease in children or younger adults occurs as a late complication of primary infection, usually within 6-12 weeks but up to ~6-9 months later, and is due to the sudden rupture into the pleural space of a recently developed sub-pleural caseous focus - thus, the sudden onset of pain seen in most patients who, having contained the organism within granulomas weeks-months before, were previously well. This is the presentation of our patient who presented with pleuritis symptoms without evidence of pneumonia. The chest pain (80%) is due to inflammation of the pleural surfaces, and the progressive dyspnea due to impairment of the mechanics of breathing by the increasing effusion.

There are 2 other presentations of TB pleuritis however that do occur in patients with active pulmonary-parenchymal TB - usually accompanied by chronic symptoms of pulmonary TB: post-primary tuberculous effusions, and tuberculous empyema. These patients most often have clinical evidence of coexisting active pulmonary TB: chronic cough, weight loss, fevers, night sweats, etc.

In both rich and poor areas of the world the proportion of pleural effusions related to "post-primary" active TB pneumonia is rising: in rich countries, primary TB is now much less frequent than reactivation TB in older adults, and in poor countries, reactivation of latent TB in HIV(+) patients is common. Chest x-rays show evidence of active pulmonary TB in 30-50% of HIV(+) patients with TB effusions, and sputum is positive in ~20% of patients. Of those with pulmonary TB who are HIV(-) in Africa, 30% have pleural effusions.

In both primary and post-primary TB, the effusion is usually the result of a hypersensitivity response to mycobacterial antigens; the organisms are few, and cultures usually negative (culture (+) in <25%). The effusion can be massive, but in 80% of patients it occupies less than half the lung field. It's almost always unilateral except in disseminated disease (10%).

Much less commonly, pleural TB results from the rupture of a tuberculous cavity into the pleural space. Occurring in a patient with advanced active disease, the cavity's contents of caseous liquefied debris teeming with organisms leads to an overtly purulent tuberculous empyema which can erode through to the skin surface over time and is culture positive.

d) Studies from some areas in Africa report that the majority of patients with TB effusions are HIV positive (80% in one Ugandan study of 142 patients in 2001). These studies report that HIV patients are sicker and have had disease longer at presentation (e.g. in the Ugandan study, in HIV (+) patients >80% had symptoms > 1 month vs. 60% > 1 month in HIV(-) patients). (N.B. This study took place in the pre-ART era in Uganda and this observation may have been related to the denial, stigma and fear of HIV which at the time was synonymous with death.)
Pleural AFB cultures are more likely to be positive in HIV patients, and HIV patients with pulmonary TB are more likely to have an associated pleural effusion (30-40%).
TB is more likely to be disseminated in HIV (+) than in HIV (-) patients with pleural TB (30 vs. 10%) and HIV (+) patients are more likely to have bilateral effusions.

Pleural effusions in active pulmonary TB in HIV patients carry negative prognostic implications, associated with a more severe and prolonged course of disease than TB without effusion.
N.B. In the pre-HIV era, even though the hypersensitivity reaction of primary tuberculous effusion most often resolved spontaneously without treatment, 65% progressed to active TB within 5 years.

5. a) What tests are indicated and how would they be of diagnostic utility in this case?
b) What tests popular in the West, would be of little use in this clinical context and why?

a) Useful tests available (sometimes) in rural Africa include:

- *HIV test: "orients" the differential diagnosis: if HIV (+), TB is most likely, but as noted above, other diseases enter the differential.*
- *Chest x-ray, with decubitus views: Indicates extent of disease, presence of associated pneumonia (TB or pyogenic), and complicated (loculated) vs. uncomplicated effusion. Chest X-ray reveals active pulmonary TB in 30-50%; bilateral effusions suggest systemic transudative processes, mentioned above.*
- *Sputum for AFB: positive in 20-50%% with TB effusions;*
- *Analysis of pleural fluid: TB effusions are lymphocytic exudates*
    - *Visual: clear, straw colored except if empyema; a clot forms on standing within minutes in a clear tube without anticoagulant due to high protein content –*

valuable test in resource-poor settings, but not invariably accurate. Serosanguinous only in 5%.

- *Cell count is between 1000-6,000/mm^3 in 60% with TB, mostly lymphocytes. Only 10-15% have >50% polies, usually in the first days of illness, but then can the PMN count can be very high; in parapneumonic effusions due to pyogenic organisms, another cause of high protein exudates, the cell count is poly predominant.*
- *Glucose < 60mg% in only 20-30%, but usually pleural < serum glucose. (pleural cancer, empyema and rheumatoid arthritis are also causes of very low glucose <30).*
- *Protein >3 g/dl in almost all, and >5g/dl in 50-70%;*
- *PPD initially negative in ~1/3, but 100% positive in 6-8 weeks;*

b)
In the developed world, the differentiation between "exudate" and "transudate" biochemically – using LDH (>2/3 upper limit of normal for serum), LDH (fluid/serum) ratio (>0.6); and protein (fluid/serum>0.5) has assumed reverent stature as the initial "test". However, it misclassifies ~25% of transudates as exudates: if an effusion meets exudative criteria but seems to be a transudate clinically AND the serum - fluid protein difference is >3.1 gm% the effusion should be classified as transudate.

In this patient, the "Light criteria" are <u>altogether unnecessary</u>: the clinical symptoms and unilateral presentation of the effusion in the absence of symptoms/findings of a systemic edematous process (i.e. clinical "tests") are ONLY consistent with diseases in the so-called "exudative" realm, and the additional (and usually unavailable) biochemistry doesn't add to the diagnostic accuracy.

In this patient, the HIV test was negative, and all other tests, including CXR, were unavailable at the time. We felt clinically comfortable with the diagnosis of pleural effusion, and a pleurocentesis revealed clear straw-colored fluid that coagulated within 5 minutes.

6. What treatment is indicated?

Pleural TB, if primary, often resolves without therapy. However, as noted above, primary pleural TB is a huge risk factor for later development of reactivation TB (65% will have active TB in 5 years), and in our case we couldn't be sure there was no underlying TB infiltrate although as discussed, there was no clinical suggestions of pulmonary TB.

The treatment for TB pleuritis is the same as pulmonary TB, and the patient was given a course of RIPE for 6 months, and as expected even without therapy, fully recovered. Steroids are without benefit.

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

H. Simon Schaaf, A Zumla; *Tuberculosis: A Comprehensive Clinical Reference* 2009, Saunders

Valdes, L., et.al T uberculous pleural effusions European Journal of Internal Medicine 14 (2003) 77–88

Ferrer, J. Pleural tuberculosis Eur Respir J 1997; 10: 942–947

Richter, C., et.al Clinical Features of HIV-Seropositive and HIV-Seronegative Patients with Tuberculous Pleural Effusion in Dar es Salaam, Tanzania *Chest* 1994;106;1471-1475

Luzze, H., et.al Evaluation of suspected tuberculous pleurisy: clinical and diagnostic findings in HIV-1-positive and HIV-negative adults in Uganda Int J Tuberc Lung Dis 5(8):746–753

Heyderman, R.S., et.al Pleural tuberculosis in Harare, Zimbabwe: the relationship between human immunodeficiency virus, CD4 lymphocyte count, granuloma formation and disseminated disease Tropical Med Int Health 1998 3 (1): 14-20