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 21 – RIGHT ABDOMINAL PAIN AND FEVER

A 29 year old man presents to the hospital with increasing right upper quadrant (RUQ) abdominal pain for 3 weeks.

A farmer who also raises goats and sheep, he was previously in good health living with his wife and 5 children until about a month ago when he began losing his appetite and having intermittent fever and sweats at night. About a week later, he began feeling increasing pain in his right upper abdomen. Over the past week the pain has gotten significantly worse, even with inspiration, and is also felt in the right shoulder. He has had a dry cough without sputum for 2 days which worsens the pain. There have been no myalgias, rash, jaundice, vomiting or diarrhea; he does not own dogs or other pets, is exposed only to goats and sheep, and has no history of liver disease, travel, medications, change in color of urine or stool, or prior pain like this.

PE: Appears uncomfortable, apprehensive, holding his belly but no acute distress

BP 110/80 RR 24 shallow T 101.5 p.o. HR 95

mouth/throat: without thrush, petechiae, or masses

conjunctivae: non-icteric, no petechiae

neck: no lymphadenopathy, jugular venous pulsations or hepato-jugular reflux

lungs: occasional crackle at the right base; dullness to percussion on right lower 1/3 lung field with egophony above;

heart: PMI in 5th intercostal space; normal S1, S2 without murmurs or gallups

abdomen: liver span 15 cm, tender medially > laterally to light percussion/palpation over a vague area of RUQ "fullness" from right of xyphoid to mid-clavicular line that descends with inspiration,

tenderness to palpation in right-sided intercostal spaces,

no spleen or other masses felt

rectal: brown, guaiac negative stool

extremities: normal strength

neurologic exam: normal cranial nerves, motor, sensory, cerebellum, reflexes and gait

Urinalysis by dipstick: s.g. 1.025, (-) for heme, protein, leukocyte esterase, nitrites; +1 bilirubin

1. What is the "frame" of the case (i.e. the key clinical features that the final diagnosis must be consistent with)?
What does each feature suggest about the disease process?

- *young male [His youth makes it less likely (but possible) that the problem is cancer. N.B Hepatocellular carcinoma presents at an earlier age in Africa than in the West.]*

- *fever and other constitutional symptoms e.g. sweats and weight loss, for a month [This constellation suggests a chronic inflammatory process.*

  N.B. Sweats happen with defervescence and signify an underlying febrile state. Thus "sweats" adds little independent diagnostic significance to the presence of the "fever" itself except to confirm it, but becomes a useful clinical clue when the patient is unaware of fever which is often the case in insidious-onset, chronic febrile conditions like TB, abscess or sub-acute endocarditis.]

- *right upper quadrant (RUQ) pain; tender area of "fullness" descending with inspiration*

[Sub-diaphragmatic organs such as liver or spleen descend with inspiration. Pancreas or kidneys, retro-peritoneal organs, do not descend with inspiration. The focal area of "fullness" which is more tender than the rest of the liver and descends with inspiration, suggests a discrete mass lesion such as tumor or abscess in the liver.]

- *No conjunctival icterus and urinalysis with +1 bilirubin*
  [The patient has had fevers and anorexia for a month, and progressive pain in the RUQ. It would be extremely unusual for any cause of diffuse hepatocellular injury, like viral hepatitis, to be that symptomatic without causing jaundice; +1 bilirubin in a concentrated specimen of urine is insignificant and non-specific, but consistent with a mild increase in serum bilirubin filtered by the kidney.]

- *associated lung symptoms of cough and pleuritic shoulder pain, with dullness to percussion over the right posterior lung field*
  [The pleuritic pain suggests an inflammatory process abutting the diaphragm, and the dullness suggests either a raised hemi-diaphragm or a pleural effusion. The cough suggests it's an effusion.]

2. What is the differential diagnosis?
What are the "pros and cons" for each disease mentioned and what is the most likely diagnosis clinically?

The differential is that of RUQ progressive pain in a young male with fever and hepatic tenderness:

- *Viral hepatitis: Viral hepatitis is suggested by symptoms of RUQ discomfort with tenderness and fever, preceded by constitutional symptoms like anorexia. However, symptomatic viral hepatitis A (HA) is relatively uncommon in Africa as most of the population are exposed and develop immunity to HA when young, this patient has no risk factors for acquisition of hepatitis B (HB) or C (HC), and hepatitis C doesn't present with sub-acute progressive symptoms. More importantly as noted, the lack of jaundice or (more significant) bilirubinuria would be markedly unusual after a month of progressively symptomatic hepatitis, and the focal tenderness, lung findings, and height of this patient's fever (101.5 p.o.) would also be very atypical for viral hepatitis.*

- *Hepatocellular carcinoma (HCC): HCC is prevalent in Africa - primarily as a complication of chronic HB and infrequently, HC. The prevalence of HB is markedly higher in Africa than in North America - sometimes acquired in utero, but most often in early childhood.*

HCC is 30-100 times more common in Africa than in the West. It can cause RUQ tenderness via invasion or stretching of the hepatic capsule, and fever – both of which this patient has. However, with HCC the symptoms are usually more insidious and evolve over a longer period of time than in this patient, fever is unusual (although seen), the liver is hard and nodular on exam, and lung findings are absent.

- *Hydatid cyst disease (Echinococcus granulosus): Hydatid cysts, caused by the larval stage of the echinococcus (a cestode parasite) in humans, are prevalent as a cause of both liver and lung cysts in areas where livestock are raised in association with dogs.*
  Carnivorous dogs eat the meat of dead livestock (or humans), the intermediate hosts of the echinococcus, ingesting any hydatid cysts embedded in their tissues. Hydatid larvae hatch in the dog's intestines, attach to the mucosa, and develop into adult worms. The adult worms produce eggs and, as the "definitive host" to the adult parasite, the dog excretes echinococcus eggs in its feces. The eggs are ingested by "intermediate hosts", man and livestock (especially sheep), through feces-contaminated food and water or children playing with dogs, hatch into invasive larvae in their intestines, enter the circulation, and end up in the liver (65%), lung (25%) or rarely other tissues (bone, CNS, heart).

  The larval cysts enlarge slowly over many years without inducing an inflammatory response and often remain asymptomatic. Symptoms, when they do occur, do so because of their size and location: in the liver, insidious RUQ pain and mass, nausea, occasionally biliary obstruction and jaundice. The most serious complication is cyst rupture into the abdominal cavity or lung, often induced by trauma, which can produce anaphylaxis and shock.

  Cysts can rarely become secondarily infected, and if this patient came from a nomadic tribe living close to its dogs like the NW Kenyan Turkana or NE Ugandan Karamajong, a bacterial infection of a hydatid cyst would be a plausible diagnosis. However, such a complication is very rare, the patient does not come from such a hyper-endemic area, and he does not own a dog.

- *Liver abscess, pyogenic: A liver abscess is strongly suggested by the fever, insidious clinical course with constitutional symptoms, and focal area of RUQ pain. The clinical presentation fits this patient. However, pyogenic bacterial abscesses more often afflict older patients (>50) with comorbidities such as diabetes and/or other sources of abdominal infection such as diverticulitis or appendicitis which have seeded the liver. Nevertheless, these features are not powerful predictors, and a pyogenic abscess is possible.*

- ***Amebic Liver Abscess:*** *Entameba histolytica is an invasive, aggressive protozoan that spreads via feces-contaminated food and water, resides in the colon, and can cause either dysentery or be relatively asymptomatic with occasional symptoms of alternating diarrhea and constipation. However, through the portal circulation the amebic trophozoite can travel to the liver where it kills hepatocytes on contact inducing liquefying necrosis ("anchovy paste" without cells) and hepatic abscess formation. It's an extremely common cause of hepatic abscess in areas of poor sanitation world-wide.*

  Clinically, the symptoms of amebic abscess usually evolve over 1-2 weeks before presentation, but in 20-50% it's more than 4 weeks (up to even a year) before the patient seeks medical attention. Males, usually 20-40 years old, predominate 10:1 for unclear reasons (the ratio is equal in children). RUQ pain and tenderness are seen in 85-90% of patients; fever, often >102F and spiking, is common in acute to sub-acute presentations of weeks duration, but the majority of older adults with more chronic courses lasting months are afebrile; jaundice is uncommon (5-30%); hepatomegaly is seen in 30-50% and the right lobe is involved in 80%; >75% of abscesses are solitary, 25% multiple; only <30% have or have had recent diarrhea; the right hemi-diaphragm is elevated in most patients, often with "tenting" and associated pleural effusion due to the underlying abscess abutting the diaphragm. Complications are due to rupture: into the pleura/lung most of the time, the abdominal cavity, or the pericardium (in left lobe abscesses). The latter two are often fatal.

  This young male patient has a near-classic presentation of sub-acute amebic abscess which is now abutting the diaphragm and pleura and causing pleuritic pain. A discrete mass can't be palpated, but an area of "fullness" in the RUQ is more tender to percussion than the rest of the liver.

3. What tests can verify the diagnosis? In rural Africa?

- Ultrasound (or other imaging, CT/MRI) are nearly 100% sensitive in detecting "abscess", but no imaging technique can distinguish amebic from pyogenic abscess, both of which occur much more frequently in the right lobe.

- Needle aspiration of the abscess under ultrasound guidance is the gold standard. "Anchovy paste" without trophozoites, cells or bacteria is seen in amebic abscess; leukocytes and bacteria are seen in pyogenic abscess.

- Serology by indirect hemagglutination is 70-80% sensitive at presentation, 95% in convalescence. The main problems, besides availability, are the 20-30% false negatives, and, since the test remains positive for years, the 10-35% "background" false positive rate in

residents of developing countries. (Serum PCR for ameba antigen is being studied and is diagnostic; thus far, a sensitivity of ~ 65% or more.)

- Stool O & P microscopy: is only 10-30% sensitive in patients with hepatic abscess, and other noninvasive but morphologically identical species, E. dispar and E. moshkovskii, can cause false positives.

- CBC: in both amebic and pyogenic abscesses, the WBC is >15,000 with left shift. Ameba does not provoke eosinophilia. Anemia can be seen in both causes of abscess.

- Response to empiric therapy (see below).

4. How would you empirically treat this patient?

Treatment of amebic abscess is with metronidazole 750 mg. p.o. 3x/day x 5-10 days, PLUS a luminal agent to eradicate cysts (since over 70% of patients with amebic abscesses have cysts in the gut that can be a source of recurrent invasive infection). Oral luminal agents include iodoquinol 650 mg tid x 20 days, paromomycin 500 mg tid x 7 days or diloxanide furoate, 500 mg tid for 10 d. The luminal agent can be started after treatment for the abscess.

Importantly, patients will defervesce and feel much better after only 3-4 days of therapy, often after 1-2 days. Such a response can be used diagnostically since pyogenic abscess will not usually respond to a single agent as quickly. N.B. Paradoxically, ultrasonographic resolution of amebic abscesses takes months and only 30% resolve within 6 months; on the other hand pyogenic abscesses resolve in 4-6 months in 95% of those treated with antibiotics and drainage.)

Aspiration of even large abscesses has been shown to be of <u>no benefit</u> in the resolution of uncomplicated amebic abscesses. Aspiration should be reserved for patients in whom the initial diagnosis is uncertain due to clinical risk factors of pyogenic abscess; who don't respond to therapy in 5 days or who are deteriorating; in whom rupture seems imminent by imaging; or when a large left hepatic lobe abscess is abutting the pericardium. Rupture into the pleural space is an indication for percutaneous drainage of the pleural space, and rupture into the peritoneum, for open laparotomy with drainage.

In district hospitals without ultrasound capability, <u>very sick</u> patients with a history and exam compatible with hepatic abscess should be treated for <u>both</u> amebic and pyogenic abscess promptly: to metronidazole, add a 3rd generation cephalosporin or a floroquinalone. If recovery is rapid within a few days, consider withdrawing all but the metronidazole and monitoring. If recovery persists, it's an amebic abscess successfully treated.

If symptoms recur, add back the additional antibiotic and consider transport to a hospital with percutaneous drainage capacity. If that's not possible, OR if recovery was slow or non-

definitive while on both antibiotics, continue treating with multiple antibiotics for 4-6 weeks. (Ampicillin and a first generation cephalosporin, which would cover Klebsiella, can substitute for the floroquinolone or 3rd generation cephalosporin if necessary.)

Suggested Reading:

Salles, J.M. et.al, Hepatic Amebiasis Brazilian Journal of Infectious Diseases 2003;7(2):96-110

Chuah, S.K., et. al, The Prognostic Factors of Severe Amebic Liver Abscess: A Retrospective Study of 125 Cases Am. J. Trop. Med. Hyg.. 46(4), 1992, pp. 398-402

Sheen, I.S. et al. Resolution of Liver Abscesses: Compariason of Pyogenic and Amebic Liver Abscesses Am. J. Trop. Med. Hyg., 40(4). 1989, pp. 384-389

Lodhi, S., et. al Features distinguishing amoebic from pyogenic liver abscess:

a review of 577 adult cases Tropical Medicine and International Health (2004) 9 (6): 718–723

Haque, R, et al. Amebiasis N Engl J Med 2003;348:1565-73.

Petri, W., Singh, U., Diagnosis and Management of Amebiasis; Clinical Infectious Diseases 1999;29:1117–25