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 Katherine Unger at kunger@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 52 – Skin and Bones

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A 19 year old woman from Northern Rwanda presents with a history of multiple “bumps” that had developed over the past 6 years in different parts of her body, and a concern that she may have cancer.

She first became ill about 6 years ago when, after feeling weak for some time, she presented with difficulty breathing climbing hills. She was told she had a problem with her heart and was treated with digoxin and Lasix. She had no orthopnea, PND nor edema at the time. She improved after about a week and returned home, although still felt weak. A few weeks to months later, she began noticing bumps and swellings in different places on her body. Most of the bumps were not tender, but some, as they slowly grew larger over months, became mildly tender to deep pressure. Other slight swellings later formed a “hole” (a skin ulcer), with minimal tenderness. The doctors at one hospital cut into one of the soft bumps on her forehead and some fluid came out but she was told that she should not have anything done to the other bumps. Since then, bumps have formed in different locations at different times often forming hard, knobby and crusted growths along both sides of her nose, the front of both lower legs, and more recently her left hand. The newest uncomfortable bump is on the front of her chest. The bumps, horns and ulcers ooze yellow fluid but haven’t recently for over a year.

She thinks she has had intermittent but not daily fevers. She feels very weak and has used a walking stick for the past few months. She has lost unknown amount of weight over the past few years and never had a menstrual period. She has no cough or problems with bowels or urine. She works, when she can, as a farmer.

She improved with medications during her initial presentation with shortness of breath 6 years ago, and doesn’t consistently take medication for her heart anymore. She has not received any treatment that improved the bumps, crusts or ulcers although papers she carries indicate that she was treated with courses of both ampicillin and doxycycline multiple times and occasionally hospitalized for up to a month and treated with antibiotics, all without effect.

Physical Exam: Cachectic young woman
T (max) x 2 days, 100.2 p.o.;  HR 105  RR 20  BP 95/60  Wt: 30 kg  Ht: 58 inches; BMI: 13.8

Skin: [SEE PHOTOS, face not included]
no petechiae, roth spots, splinter hemorrhages, etc.
R naso-labial fold under R eye 1x1.5 cm ulcer, and linear ulcer .5 x 1.5 cm under L eye, mildly swollen and tender, hard edges and center with horny protrusions
Anterior left aspect of sternum with approx. 5 x 5 cm area of bogginess, +1 tender to palpation
L. hand at ulnar aspect, enlarged, deformed, boggy to palpation with 2 thick horny projections, minimally tender/warm; and discreet non-tender 1.5 cm ulcer with hyperpigmented halo;
Tibias: bilateral anterior superior horny projections emerging from 1-2 cm ulcers, non-tender; partially surrounded by hyperpigmented halos

Eyes: fundi benign, without lesions; conjunctiva non-icteric; Mouth: no lesions, thrush, petechiae
Neck: no thyroid palpable; shoddy (<1cm) scattered cervical, axillary, inguinal LAD; no JVP or HJR
Heart: PMI forceful, brisk, 0.5-1 cm lateral to MCL, 9 cm from mid-sternum; S1,S2, regular; 4/6 murmur equally loud at LLSB and apex; pansystolic; radiating to axilla, no S3, S4;
Lungs: clear to auscultation and percussion bilaterally
Abdomen: soft, non-tender, not distended, liver 2 cm below LCM, span 11 cm; no spleen palpated
1. **What is the clinical “frame” of this case i.e., the key features of the patient’s history and exam that the final diagnosis must be consistent with?**

   - young, with disease starting at age 13, now 19
   - progressive illness over 6 years
   - skin and bone involvement, with discreet foci of disease developing over years
   - firm ulcer edges, hard horny growths, minimal heat/tenderness over lesions, with surrounding hyperpigmentation
   - weight loss, progressive weakness, history of “fevers” with low-grade fever noted
   - multiple treatment courses with antibiotics without improvement
   - loud pansystolic murmur radiating to axilla (MR), and history of “heart problem” but without symptoms or signs of heart failure years later on no medications
   - no symptoms or signs of disease in lungs, liver, or brain.

2. **What patho-anatomic process is suggested by the clinical “frame”?**

   The marked weight loss/cachexia suggests a chronic catabolic process, and the fever suggests inflammation. The 6 year history of progressive and widespread disease essentially rules out infection with pyogenic organisms which would follow a more aggressive course. The time course also makes malignancy equally unlikely: cancer in this young girl would have to have been widely metastatic over many years without causing either death or clinical involvement of organs that receive a large amount of blood and are common foci of metastatic disease - lungs, liver or brain. The indolent course of disease is most consistent histologically with lymphocytic or granulomatous, rather than neutrophilic, inflammation.

   Clinically, the disease appears localized to skin and bone, involving very discreet foci in both types of tissue – a pattern that suggests infection with indolent bacteria or fungi (rather than viruses) that have tropism for these tissues. The degree of cachexia and weakness as well as the (probable) fever suggest that the infection is deep-seated and not likely to be isolated to skin alone.

   In summary, the clinical features suggest that this adolescent has suffered the relentless progression of an indolent, non-pyogenic, resistant infection spreading hematogenously, inducing chronic inflammation in discreet foci in skin and bone.

3. **What is the probable significance and relationship to the present illness, of the heart murmur and “heart problem” diagnosis made on first presentation 6 years ago, weeks-months before these lesions appeared on her skin? Explain.**

   There are 3 possible ways to explain the occurrence of the “heart problem” and her present illness:

   a) **Causal**: the heart murmur is/was a sign of subacute endocarditis (SBE) which seeded the skin and bones over time;
b) Unassociated: this African girl of 13 had underlying rheumatic heart disease causing the loud murmur (mitral regurgitation clinically), and then acquired independently an unrelated infection that caused the skin/bone disease and her constitutional symptoms.

c) Associated, but indirectly through “detection”: The symptoms of one disease (bone/skin) led to the detection of the other (murmur), and subsequent misdiagnosis of the underlying problem.

a) Causal: It’s clinically implausible that underlying SBE could explain the patient’s course. Six years is too long for even the most indolent organisms in SBE; her heart disease didn’t progress and she is not in heart failure despite never having been treated for SBE (that we’re aware of); whether or not she was treated with prolonged antibiotics for SBE in the past, the skin-bone lesions and constitutional symptoms continue to evolve; the lesions are not the hot/tender (neutrophilic) abscesses seen with multiple pyogentic emboli; the emboli would not be restricted to bone/skin without clinically involving organs like lung, brain, etc. that receive most of the blood flow.

b) Unassociated: In Africa, lack of access to care and a very high disease burden often meet in patients who present with 2 diseases simultaneously, or nearly simultaneously. This is probably close to what occurred in this patient.

c) Associated through “detection”: It is quite plausible that the murmur and “heart problem”, although not causing her illness, are nevertheless associated with it clinically as follows:

At age 13, her “skin-bone disease” took hold and hematogenously disseminated, first causing vague symptoms of weakness and unusual fatigue when walking up familiar hills. She described these symptoms as “difficulty breathing” (or they became “difficulty breathing”) when she was seen by a medical provider. The otherwise asymptomatic murmur was then noted on exam and her symptoms attributed to the “heart”. The more specific manifestations of her underlying inflammatory disease only became obvious in the skin weeks later.

It would be extremely unlikely that the “heart problem” behind her loud murmur caused her “difficulty breathing” 6 years ago and, while going essentially untreated, didn’t cause florid CHF and a huge heart in the meantime. Given the hindsight of 6 years, she probably never really “improved” with digoxin and diuretics but rather adapted over time to her indolent, debilitating, infectious - but non-cardiac - illness.

However as in the past with this patient, the very loud murmur will always draw clinical attention and tempt the diagnostician to make a causal link between the heart and the non-specific constitutional symptoms of the (other) underlying disease. Although such hypotheses are entirely appropriate early in the diagnostic process, ultimately they must be “verified”: i.e. the final diagnosis must be parsimonious, coherent and comprehensive while explaining all the important clinical features of the “frame”. Implicating her heart problem as the cause of her present illness fails this step of “diagnostic verification”.

4. a) What is the differential diagnosis in this case, and the most likely diagnosis?
   b) What are the key features of each of the diseases in the differential?
   Defend your choice of the most likely diagnosis.

a) The differential diagnosis involves chronic inflammatory conditions, both infectious and non-infectious, of bone and skin:

- African Histoplasmosis, an uncommon fungal disease endemic to the area;
- Yaws, a spirochete (treponeme)
- Mycetoma, a chronic infection of subcutaneous tissues caused by either filamentous bacteria (actinomycetes) or true fungi.
- Tuberculosis of bone and skin
- Subacute Bacterial Endocarditis
- Non-bacterial Osteitis (NBO) or Chronic Recurrent Multifocal Osteomyelitis (CRMO)

### African Histoplasmosis:

The most likely diagnosis on clinical grounds is **African Histoplasmosis** characterized by granulomatous and suppurative lesions in cutaneous and osseous tissue. Two forms of histoplasmosis exist in Africa, *H. capsulatum* (as in the American Midwest and the Caribbean), and *H. duboisii*, endemic to Africa alone and known as “African Histoplasmosis” (AH). Whereas *H. capsulatum* most commonly involves the lungs, *H. duboisii* involves the skin, subcutaneous tissue and bones preferentially.

AH has been reported from about 20 countries in equatorial Africa, from 20 degrees north of the Equator to 20 degrees South, and from Senegal to Tanzania. Most reports originate from Nigeria, Niger, Senegal, Congo and Uganda – from regions with high rainfall, humidity and little variation in diurnal temperature. All ages are affected, but peak incidence occurs in the teenage years and more commonly in agricultural workers, carpenters and others engaged in outdoor activities. In endemic regions approximately 3% demonstrate serum reactivity to *H. duboisii*, but the antigen also cross-reacts with *H. capsulatum*. In some regions up to 35% manifest skin sensitivity.

AH skin involvement takes the form of papules, nodules, ulcers and psoriosiform lesions. Nodules and papules often have a surrounding hyperpigmented halo considered pathognomonic, and as the growths enlarge the center ulcerates. (Both halos and ulcers were seen in this patient.) Subcutaneous abscesses present as firm, tender swellings that can discharge pus. Ulcers and sinus tracts can also be signs of extension from underlying osteomyelitis.

AH has a predilection for bone marrow, with multiple osteolytic lesions resembling myeloma seen in the tibia, humerus, femur, vertebrae, wrist and skull. The lesions can have osteoblastic foci as well. With extension to the periosteum, a tender painful swelling appears. Involvement of contiguous spinal cord or joints can occur. Local lymphadenopathy is common, and can be diffuse in disseminated disease. Liver, spleen, or intestinal mucosal involvement can present with jaundice, diarrhea, obstruction and/or perforation. These GI manifestations as well as lung disease are rare in most reports: cutaneous and osseous disease is most common. The disease can slowly progress for years causing the constitutional symptoms seen in this patient, or wax and wane and even spontaneously remit over time.

In this patient, her age, residence in an endemic region of Africa, and outdoor exposure make the diagnosis of AH plausible; the weight loss, fever, chronicity of disease, and slow progression are consistent with the natural history of AH, a chronic fungal infection inducing granulomas; and the predilection for bones and skin in non-contiguous, multifocal locations with characteristic if not pathognomonic lesions is nearly diagnostic of AH clinically.

**Yaws** is tropical disease of children usually younger than 10, caused by the spirochete *T. pallidum* subsp. *Pertenue* that induces serologic responses (VDRL, FTA, etc.) indistinguishable from syphilis. It causes a wide variety of skin manifestations, lymphadenopathy and periostitis of bone. It was nearly eradicated from Africa in the 1950s through massive antibiotic inoculation campaigns, but has been re-emerging in the past decades in the warm humid topics of Africa, Asia and Latin America. (N.B. These inoculation campaigns of the ‘50’s nearly eradicated yaws but used unsterilized needles in the process. Proposed as a model debacle of public health programs, the eradication campaigns have recently been implicated in the evolution of the AIDS virus by facilitating, through dirty injections, mutations in a pathogenic strain...
of simian immunodeficiency virus. As the theory goes, HIV-1 and HIV-2, quite distinct viruses from East and West Africa respectively, both “jumped” nearly simultaneously from different species of monkey to man during continent-wide injection campaigns. The injection frenzy quickly enabled, via serial passage of blood mixing repeatedly in re-used needles from sequential human hosts, progressive biological adaptation to humans and finally the evolution of mutant strains transmissible between humans - - HIV-1 and HIV-2.)

Yaws begins with a primary papular lesion that enlarges into a papilloma several centimeters in diameter called a “mother yaw”. The moist mother yaw weeps with spirochetes and resolves after 3 to 6 month. During this time the treponeme disseminates locally and hematogenously to other areas of skin, lymph nodes, cartilage and bone. Clinically, papules, nodules and hyperkeratotic skin lesions; tender lymphadenopathy and swelling of bone and cartilage appear. In untreated disease, infectiousness lasts 12-18 months and secondary recurrences persist for up to 5 years before remission occurs. Cutaneous lesions remit without scarring. The disease is very sensitive to penicillin.

The low prevalence of active yaws in the population combined with the clinical features of patient age, duration of progressive disease, and lack of response to antibiotics rules out Yaws in this patient.

Mycetoma is a firm subcutaneous swelling, usually painless or minimally tender, which enlarges and extrudes through deep sinuses granular aggregates of the causative organisms to a smooth, shiny skin surface. It is caused by various organisms categorized as either aerobic actinomycetes – filamentous bacteria – which cause actinomycetomas with ill-defined margins that penetrate surrounding tissues, or true fungi – which cause eumycetomas which are mobile. If the grains are black or brown, the cause is a fungus as bacteria do not produce melanin. If they are white/yellow, they may be caused by a fungus or an actinomycete.

The infection starts in the skin and invades underlying subcutaneous tissue and bone. It spreads to nearby tissues through facial planes and rarely through lymphatics, not hematogenously. The lower limbs, usually the feet, are involved in 75% of cases, the hand in about 10%. It is rare to have a mycetoma in more than one location.

This young woman didn't have mycetoma: although bone and skin were involved with minimal tenderness, the multifocal widespread distribution of lesions, lack of sinuses with grainy exudates, and her significant constitutional symptoms paint a composite picture incompatible with mycetoma.

Tuberculosis of bone and skin: Tuberculosis can affect both bone and skin. Osseous TB represents about 1-4% of cases of TB, and 10% of all cases of extrapulmonary TB. Half of the cases involve the spine and the other half the peripheral skeleton, most commonly the legs; usually a single site is affected with over 80% of osteoarticular TB involving both the metaphysis of bone and the adjacent joint. The disease has an insidious onset, progresses slowly, and diagnosis can be delayed 1-2 years. Many but not all have constitutional symptoms. Multiple simultaneous osseous lesions are rare and usually seen in immune immature or compromised hosts.

TB of the skin presents with insidious progression of a wide array of lesions: papules, pustules, nodules, violaceous plaques, verrucous lesions, ulcers, chronic sinuses, necrotic lesions, and scars. Lupus vulgaris lesions are apple-jelly colored nodules and plaques in reaction to TB spread hematogenously from internal organs in hypersensitive hosts, thus the organism is rarely isolated. Other manifestations of cutaneous TB are caused by extension from underlying nodal or osseous infection. Rarely crops of multiple, umbilicated papules or pustules can be a sign of late miliary TB.

Although TB is a chronic granulomatous infection that can involve both bone and skin, the timing, pattern and distribution of lesions in this patient would be extremely unusual. While TB can involve bone and skin, it has no particular predilection for these sites. The multifocal nature of this patient’s disease implies hematogenous spread, but even after many years there is still no sign of
infection in organs that are much more commonly involved in disseminated TB such as lung, kidney, liver or brain. TB is highly unlikely.

Subacute Bacterial Endocarditis with embolic lesions causing skin and bone disease: (very unlikely clinically, as discussed above, see #3).

Non-Bacterial Osteitis (NBO) and its sub-classification, Chronic Recurrent Multifocal Osteomyelitis (CRMO) are characterized by multiple foci of non-bacterial osteomyelitis that present usually in childhood (around age 10) with a mix of osteolytic/sclerotic lesions thought to be autoimmune in nature. Other inflammatory associations suggest that NBO/CRMO is a pediatric “SAPHO” syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). About half of the bone lesions involve the vertebrae. 85% of cases are relieved with NSAIDS.

Besides its rarity, clinical features mitigate against NBO/CRMO in this patient: patients with NBO are generally well, without fever, weight loss or fatigue; the skin lesions are more superficial (pustules), and the duration of illness is usually less than 2 years, with a range of 1-4 years.

5. What tests are available in rural Africa to confirm the most likely diagnosis, and how accurate are they?

Serologies are non-specific in endemic areas, and cross-reactions of H. duboisii with H.capsulatum occur.

Culture of the organism is difficult, insensitive, taking up to 6 weeks to grow, and not available in rural Africa.

Confirmatory tests rely on visualizing the H. duboisii yeast forms in tissue biopsies or pus from draining sinuses. The yield is high only if such specimens can be obtained and directly examined.

6. a) In general, what principles of empiric therapy should guide treatment?

b) What would be the drawback of treating multiple illnesses at once in this patient?

c) What strategy would you choose in caring for this patient and why?

a) In choosing empiric therapy, consider both the “most likely” and the “most dangerous” potential diagnoses, and the following clinical parameters: severity of illness; how fast the disease is clinically progressing and the natural history with and without therapy of the various diseases in the differential; the efficacy, cost, duration, and time to response of potential therapies.

In general, if the patient is very sick, i.e. could die within days if the wrong treatment is chosen initially, treat not only the most likely and the most dangerous, but ALL reasonable possibilities. When empirically treating more than 1 disease, have a strategy for the longer term:

- if both (all) diseases can be completely treated within a week or so, there is rarely any need to pare down treatments later: complete therapy for all diseases;
- if treatment duration, expense and/or toxicity vary among diagnoses, treat for all until the patient stabilizes and shows improvement. After improvement, continue treatment for the most likely disease possibility while monitoring closely for resurgence of other (less likely) ones for which therapy has been withdrawn. (Of course, modify and adapt the specific strategy to the case: e.g. one might continue 2 of 3 regimens if there are 2 equally probable diagnoses, and/or if the 2nd most likely diagnosis has a short duration of therapy, etc.).
In a similar vein, if 2 diagnoses are each equally probable but one is an indolent disease requiring long term therapy, relapse of which won’t kill immediately, once the patient improves after days of broad “shotgun” therapy and is stable, step back. Deciding to continue treatment for the more aggressive option (e.g. pyogenic pneumonia) while suspending treatment for the more insidious disease (e.g. TB) while observing closely for symptomatic relapse - is prudent.

If moderately sick, i.e. has “reserve”, will survive if the correct therapy is withheld for at least 3-5 days: treat for ONE diagnosis at a time. [This is the situation in this patient.]
- Treat for the “most likely” if the natural history of the “most dangerous” is such that its treatment won’t be compromised or more complicated after a delay of days;
- Treat for the “most dangerous” if its response to therapy will be more quickly and clearly interpretable, and the delay won’t compromise treatment efficacy for the “most likely”, if necessary, later. This is the approach recommended for tuberculosis in HIV (-) patients: when pulmonary TB is suspected, first treat for pyogenic pneumonia (“most dangerous”, i.e. acute), even if less likely than TB, with 1 and possibly 2 courses of different antibiotics while collecting sputum for AFB smears; if smears are AFB +, treat TB; if smears are negative and there is no response to antibiotics, then treat for TB (ideally, after an x-ray shows an infiltrate).

If “mildly” sick: You don’t have to treat immediately! Consider withholding all treatment and following the patient in the hospital for days while carefully observing for more specific signs to appear, or the patient to spontaneously improve (which is common).

Other things being equal (though they never are!):
- Treat diseases with an indolent course last, among reasonable options;
- Treat diseases with a shorter time to measurable therapeutic response first or earlier in the sequence;
- Treat diseases with a long duration of therapy (e.g. TB, Brucella) last in the sequence

b) The drawback of treating multiple illnesses at once in this patient is the difficulty of knowing which treatment is working and thus which to continue.

If therapy for TB, histoplasmosis, SBE and mycetoma were all short duration treatments with no toxicity, this question would not be clinically important. However, that’s not the case. For example, treating TB implies multiple drugs for a long time; and with fungal disease this extensive, treatment is longer than 1 year. A response to shotgun therapy for both TB and histoplasmosis may imply having to keep all drugs going for their full course, risking drug interactions and common side effects. Alternatively, if one tries to pare down later but chooses the wrong single treatment to continue, the prior partial treatment the patient received (for the right diagnosis) will result in a delayed relapse of that disease – one likely to be subtle and confusing clinically and more difficult to diagnosis objectively.

Furthermore, in “real life” in Africa, either she or one of the multiple practitioners who will care for her over time will probably diverge from the plan after a few months, especially when she is feeling better (or when having to pay for some of the drugs as an outpatient). They will then cut down to treat the disease they are used to treating – TB – the far less likely option. These would be risks worth taking if she was deathly ill or the process was acute. However in this case, the process has been insidious over 6 years, she is not on death’s door, and the treatment of the most likely diagnosis (Histoplasmosis) can be assessed after 1-3 weeks.

c) The strategy should be to treat African Histoplasmosis, alone, and monitor for a response which should be clinically obvious within 1-3 weeks.
The problem is that there isn’t a wealth of data on the most effective therapy: Amphotericin works, but is toxic and expensive. Fluconazole works sometimes, but not always; ketoconazole is better than either itraconazole or fluconazole according to most reports. There have been gratifying responses to trimethoprim-sulfamethoxazole (Septrim). Since Amphotericin works, it is probably best to treat with it during an empiric trial of therapy that will be used for diagnosis. If a response is seen within 3 weeks, then the diagnosis of AH is almost certain. One can now begin treatment with Septrim for the long term; if clinical deterioration occurs, Amphotericin can be re-started and treatment completed with Ketoconazole. (In district hospitals, ketoconazole would have to be specially procured, and could be during the re-treatment phase with Amphotericin.)

**Suggested Reading:**


Loulergue, P., et.al; Literature Review and Case Histories of Histoplasma capsulatum var. duboisii Infections in HIV-infected Patients (2007) Emerging Infectious Diseases 13, No. 11, 1647-52


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