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 43 – The Ulcer that Won’t Go Away

A 15 year old boy presents with a gradually increasing non-healing ulcer of his skin. He was well until 3 months ago when he fell off his bike into a muddy puddle of water, scraping his right knee and lower leg. The scrape healed, but about 2 weeks later a small lump appeared over the inner part of his lower right leg just above the ankle. The lump was not tender; he had no fever and was able to work, bike, and play normally. Over the next 1-2 weeks the lump increased in size to about 2 cm, with surrounding swelling and overlying shiny skin with some scaling.

About 2 months ago, the skin opened and liquid oozed out. His mother wrapped the wound with a bandage and he went to work in the fields. The wound gradually increased in size, and continued to drain fluid. He went to the health center where the wound was washed and cleaned, covered with a purple liquid (gentian violet), and dressed with clean bandages. Over the next 1-2 weeks it didn’t go away but didn’t hurt either, and he was able to continue his activities. When it continued to increase in size, he went back to the health center where the wound was again cleaned, new bandages applied, and antibiotics (?name) were prescribed to take for 2 weeks.

When the antibiotics didn’t help, he came to the hospital accompanied by his father. He hasn’t had fever, weight loss, decreased appetite, or anything like this before.

Physical Exam: Looks well, normally thin, in no distress.

V.S: BP 100/70, HR 82, T: 98.5, R: 14
Mouth: no thrush
Neck: no lymphadenopathy
Lungs: clear; Heart: normal S1, S2;
Abdomen: no hepatosplenomegaly or masses;

Extremities: right lower leg, above medial malleolus, 12 cm oval ulcer, ½ to 1 cm deep, with white-yellow base and sharply delineated thickened margins with undermined edges (in places), with surrounding induration, hyperpigmentation; non-tender.
Otherwise, extremities and skin normal.
1. What’s the “frame” of this case (the key clinical features the final diagnosis must be consistent with), and the clinical significance of each item in your frame?

- Lesion developed post-skin abrasion: suggests an environmental pathogen introduced through the skin.
- Single lesion: suggests dermatologic origin of the disease rather than a systemic origin with secondary dermatologic involvement.
- Chronic, increasing for 3 months: a very indolent process, so unlikely to be an infection with a pyogenic organism, yet too rapid for neoplasia: likely chronic granulomatous or non-inflammatory necrotizing pathology
- Non-tender, no fever: non-pyogenic organism without much inflammation; or a neoplasm.
- Started as firm/non-tender nodule under the skin before “opening” and discharging fluid: suggests an infection causing undermining necrosis with secondary ulcer formation rather than a primary ulcerating process

2. What is the differential diagnosis of the leg ulcer in this boy, the pros and cons of each disease mentioned vis-à-vis this case, and the most likely diagnosis?

- “Tropical Ulcer”: Tropical phagedenic ulcers, called a “disease of the poor and hungry”, are caused by necrotic reactions induced by anaerobic bacteria, principally fusobacteria (F. ulcerans) together with Treponema vincenti, which are introduced into the skin by minor trauma. They occur on the legs, begin as a small papule or vesicle which rapidly breaks down into a usually very painful, sharply defined ulcer with a slightly indurated edge, and can either be rapidly aggressive with deep penetration, or become chronic. Both the longer time course of development and the painless nature of the ulcer in this case, make tropical ulcer extremely unlikely.
- Tuberculosis, Cutaneous: TB of the skin is a rare complication which presents in various forms, some of which can ulcerate. The lesions of lupus vulgaris (red-brown “apple-jelly” nodules and papules around the neck/face), scrofuloderma (extension to the skin from underlying TB of the lymph nodes), primary cutaneous (papule which ulcerates and drains into reactive regional nodes) are all rare forms of TB which can sometimes form ulcers – usually smaller ulcers than in this case, even more indolent, located on the upper body, and often associated with other manifestations of underlying TB.
- Cutaneous Leishmaniasis: Leishmania are obligate intracellular parasites introduced by the bite of sandflies in North and East Africa (in the Sudan, Ethiopia, Kenya, and bordering areas in northern Uganda), South Asia, the mid-East (especially Afghanistan) and Central and South America. The parasites infect reticuloendothelial cells of the skin, mucosa or liver/spleen/nodes causing cutaneous, mucosal or visceral (kala-azar) forms of disease. Cutaneous disease begins as a papule at the site of the sandfly bite, which can
enlarge, become a nodule or plaque, and/or progressively ulcerate over 2 weeks to 6 months. The ulcers, which can be multiple and clustered, are painless, with raised margins and a flat base of granulation tissue without overt pus (unless secondarily infected), and depending on the infecting species, can appear less or more inflamed, “dry” or “wet”. They usually occur on the face or extremities, are associated with local lymphadenopathy ~ 10% of the time, spontaneously heal over months to a year or more, and leave scars. In this case, the geography (Southwest Uganda) does not fit the range of the vector of Leishmaniasis, and the ulcer here appears deeper and had a preceding course as a nodule under the skin rather than an expanding crusted papule/plaque characteristic of ulcerative cutaneous Leishmaniasis.

- **Yaws**: Yaws is caused by Treponeme spirochetes spread by direct contact, a disease of children with peak incidence at 2-10 years old, seen in humid areas of equatorial Africa, South and Central America, and South Pacific. The initial pruritic papilloma is several cm in diameter from which spirochetes are spread both hematogenously and through secondary contact causing macules, papules, nodules, and/or hyperkeratosis - any of which may ulcerate. Lesions resolve after months, can recur for up to 5 years, and heal without scarring usually. However, extension to bone can cause osteitis and cartilage destruction with deformity.

- **Anthrax**: Caused by a gram positive bacillus that infects animals and forms spores that are deposited on the soil and inoculated into the skin. First a papule forms, is surrounded by vesicles, and ruptures into a 0.5-3 cm depressed ulcer with a brown-black thick adherent eschar with surrounding edema; non-tender. The timing, lack of eschar, and size of the ulcer in this patient is inconsistent with anthrax.

- **Ecthyma**: A complication of (epidermal) impetigo, ecthyma is a staph or strep infection of the dermis which forms a superficial erosion/ulcer capped by an adherent black crust that is tender. In this case, the lesion began as a nodule, and is too large, non-tender, and without an eschar.

- **“Buruli Ulcer” (Mycobacterium Ulcerans)**: This is a classic presentation of Buruli Ulcer (BU) caused by Mycobacterium Ulcerans, the 3rd most common mycobacterial disease in the world after TB and leprosy. BU causes massive disfiguring ulcers which destroy lives and livelihoods. It’s endemic in remote areas of rural Africa, particularly West Africa but also quite common in Uganda where it was first discovered (named after Buruli County in SW Uganda). BU has been designated one of the 13 “neglected tropical diseases” of the world by the WHO.

BU affects both genders equally, predominantly children, median age 15, but with a second peak in the elderly. It involves predominantly the limbs (80%). M. ulcerans is thought to live at the bottom of muddy puddles of stagnant water, or to colonize biofilms, and has been found in aquatic insects and even mosquitos. The mode of transmission is unclear, but is thought to be through skin penetration and is not contagious.
M. ulcerans produces a toxin, mycolactone, which induces necrosis and ulceration in the subcutaneous fat, and suppresses inflammation. Once the organism is introduced into the skin, the clinical lesion (as in this case) usually starts as a firm painless nodule with surrounding edema that may be pruritic, and later breaks down into a painless ulcer with well-demarcated borders and undermined edges. Depending on organism virulence and host resistance, the ulcer may remain small and discrete, or spread steadily over months to years involving entire limbs or hemi-thoraces before “burning out” and spontaneously healing - leaving disfiguring scars and contractures in its wake. Satellite ulcers with intervening islands of irregular undermined skin are common.

Besides the common nodule, other non-ulcerative forms of M. ulcerans infection include plaques (firm, elevated, well-defined with irregular borders, which may ulcerate late in a stellate pattern), and simply edema (diffuse, painless, non-pitting, firm, with vague margins) heralding a very severe form of the disease with rapid subcutaneous spread of necrosis which can acutely break down and expose a huge ulcer with undermined margins. In BU, inflammation is suppressed, and fever, late tenderness or reactive lymph nodes suggest secondary bacterial infection.

3. What complications can be seen with this disease?
   - Secondary infection with sepsis, or tetanus - either of which can lead to death.
   - Osteomyelitis, either by direct extension from the skin or hematogenous spread.
   - Disfigurement from scar formation is the most common chronic complication. When a BU extends over a joint, contracture results which limits movement and ability to work.
   - Squamous cell carcinoma can develop, especially in non-pigmented lesions.

4. How should this patient be treated?
   - Surgery, with debridement and excision of infected tissue has been the mainstay of treatment, and is the recommended approach with small lesions.
   - For large lesions such as this one, the WHO currently recommends 8 weeks of antibiotic therapy with rifampin (10 mg/kg) and IM streptomycin (15mg/kg), possibly supplemented by surgery.

In Africa, the need for daily IM injections for 8 weeks (with a medication that may cause hearing impairment and vertigo and is contraindicated in pregnancy) is a major obstacle to treatment. Studies are underway combining rifampin with ciprofloxacin. Prescribing rifampin as a single agent apart from the RIPE combination is often impossible given fears of resistant TB developing.
Suggested Readings:

Engelkens, H.J.H., et. al., Nonvenereal Treponematoses in Tropical Countries  Clinics in Dermatology 1999;17:143–152
WHO: Buruli ulcer: a pocket guide for community health workers
Sizaire, V., et. al Mycobacterium ulcerans infection: control, diagnosis, and treatment Lancet Infect Dis 2006; 6:288–96