Introduction:

Welcome to the 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 4-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. A month 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

About the Author:

I'm a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York, where my career has centered on medical education for the past 40 years – as a past residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and global health advisor and program leader at the school. I've served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. I spend about 3-4 months a year in Uganda working on the Medicine wards of Kisoro District Hospital which, like most hospitals in the world that serve most of the world's population, has (almost) no resources. "At the bedside", I teach Internal Medicine residents and medical students how to assimilate the elements of history, physical exam and epidemiologic probability into a diagnostic impression that, even without definitive testing, can lead to appropriate therapeutic strategies in the field.

Gerald Paccione MD
Professor of Clinical Medicine
Albert Einstein College of Medicine
110 East 210 St., Bronx, NY 10467
Tel: 718-920-6738
Email: gpaccion@montefiore.org

Case 59: Despite or Due to Kumensha

An 8 year old boy is brought to Kisoro District Hospital for high fever, headache and sore throat for 4-5 days.

He had been well, a student with good grades, until a sore throat and headache developed over a few hours while in class and he returned home from school early. At home he began to vomit.

His mother thought he felt "hot", and acquired coartem for malaria from the health center. After 2 days of continued fever, intermittent vomiting and worsening sore throat despite coartem, the traditional healer diagnosed "gapfura" and performed "kumenesha" or "crude tonsillectomy" (in which a stick was passed through the boy's nose and, with the healer's fingers probing the back of his mouth, his tonsils were scraped until they bled – expunging the spirit of the boy's ailment along with the blood and pus). His fevers, sore throat and headache continued unabated the next day, he would not eat, developed watery diarrhea, abdominal cramps, some vomiting and a soreness around his buttocks that made sitting uncomfortable. His skin darkened according to his mother, and his hands and bottom of his feet seemed swollen. He had no cough. When he became too weak to walk by himself and intermittently was not making sense to his parents, he was brought to KDH on the 5th day of illness.

Physical Exam: Lethargic, ill-appearing boy.

BP 100/60; HR: 140 and regular; T: 104.2 oral RR: 22

Skin: dry and "rough" to feel, without obvious rash but with a suggestion of increased darkness/hyperemia around 0.5- 1 mm skin protrusions/papilla, most notable on lower abdomen and flexor surfaces of arms; linear petechiae noted in the inguinal crease, and hyperemia around sacrum; fine powdery flakes of skin on cheeks and nape of neck; no areas of overt cellulitis or inflammation noted;

HEENT: Mouth: 4 petechiae noted on palate; dried blood in swollen, erythematous tonsillar pillars with exudates in some tonsillar crypts; uvula midline; tongue deeply red with protruding punctate red papillae and islands of thick white coating;

Neck: supple in all directions; 2 tender 1.5 cm upper cervical nodes bilaterally; shoddy nodes elsewhere, < 1 cm, non-tender; thyroid normal; JV pulsations normal, but only seen lying flat;

Lungs: clear

Heart: tachycardic, S1, S2 normal; Gr 1-2/6 short systolic murmur at left sternal border; normal PMI

Abdomen: normal bowel sounds, no hepatomegaly, spleen tip palpable, non-tender; no masses, guarding or tenderness;

Extremities: normal joint mobility, no peripheral edema but palms and soles slightly swollen;

Neurologic: lethargic, responds appropriately but slowly, no focal signs; reflexes +2; gait wobbly but symmetric

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

- 8 years old.
Some diseases, like the "6 childhood exanthems", are more common in childhood before immunity is acquired.
- 4-5 days of high fever, headache, sore throat.
Suggests acute infection is likely, with the portal of entry in the upper respiratory tract.
-"crude tonsillectomy" by traditional healer.
The crude tonsillectomy supports the symptom of throat pain and fever as dominant; the procedure may be a cause of further anorexia and persistent throat pain, and it may (rarely) facilitate sepsis]
- skin "darkened", buttock soreness, hands/feet swollen
Darkened skin in blacks and butt soreness in this acute context are likely to be symptoms of diffuse dermal inflammation.
- increasing weakness and confusion, vomiting, diarrhea…
These symptoms are likely to reflect the multi-system effects of inflammatory cytokines.

2. What is the significance of the *physical exam* findings?
Are any combinations of findings associated with specific disease mechanisms?

- Fever 104.2 oral: An oral temperature this high means the core body temperature is probably >105-106, i.e. hyperthermia in need of anti-pyretics and rapid cooling. Extreme temperature can be a cause of lethargy and confusion;
- Skin findings: Rough to feel with tiny papillary projections and subtle erythema: histologically these findings are associated with peri-follicular inflammation and engorgement of capillaries;
Linear petechiae in inguinal crease suggests capillary fragility induced by a toxin's effect on the endothelium, most easily observed over areas of pressure;
Hyperemia around sacrum is consistent with increased inflammation around areas of pressure, causing soreness around buttocks;
Fine powdery flakes of skin on face and neck are evidence of desquamation
- tonsillar crypt exudate is evidence of "exudative tonsillitis"
- palatal petechiae are other manifestations of capillary fragility (or thrombocytopenia), seen in viral or toxin-associated etiologies of pharyngeal inflammation
- tongue deeply red with red papillae and islands of white coating is "strawberry tongue", seen in a family of exanthems mediated by cellular toxins
- lethargy/confusion: can be due to encephalopathy induced by cytokines, encephalitis, high temperature, and/or volume depletion

"Strawberry tongue", acral erythema with desquamation, erythematous eruption with perineal accentuation are all seen commonly in diseases mediated by exotoxins - stapholoccal or streptococcal exotoxins as in toxic-shock syndrome and scarlet fever, and Kawasaki Disease (KD), the pathogenesis of which is unknown.

3. What *non-antibiotic* treatment should be provided promptly?

Anti-pyretics such as acetaminophen, and cooling with sponge bath and fanning to lower body temperature;

Fluids: with defervescence, vasodilatation will occur and BP may drop to shock levels unmasking the likely-marked hypovolemia from insensible losses, vomiting and diarrhea, and compromised oral intake during the last few days of illness.

4. What is the *differential diagnosis* in this case? Identify and describe the *principle clinical features* of your selections.
What is *most likely* diagnosis in this patient? Why is it most likely and what is its pathogenesis?

Erythematous rashes are very difficult to identify in black-skinned people. In general, in diseases that are associated with rash, rash is reported only 15-40% as frequently in blacks versus whites. Thus the clinician has to look carefully with heightened diagnostic suspicion for skin involvement in febrile African patients. In this patient, the rough texture, flaky desquamation of the face, and darker tint around the perineum and buttocks all suggest inflammatory skin involvement.

Diffuse erythematous rash with fever is compatible with a long list of inflammatory diseases caused by a) viruses; b) bacterial exotoxins; c) drug allergies; d) other blood-borne infections such as rickettsioses (rocky mountain spotted fever), borrelia (Lyme), etc. and e) systemic auto-immune diseases such as lupus, Still's disease, etc.

Narrowing the myriad possibilities for "rash and fever" requires appreciation of the epidemiologic prevalence, demographic spectra, and associated clinical manifestations in <u>other</u> organ systems of the various diseases in the differential diagnosis. Even then, a specific diagnosis cannot be made clinically most of the time. Fortunately however, a specific diagnosis is NOT required most of the time, as the majority of such afflictions are self-limited with complete recovery the rule. In general, even the more "dangerous" diseases associated with fever and rash, i.e. the ones that can be fatal, are fatal infrequently with rare exceptions (like Ebola). Furthermore, in ultimately fatal cases, the more serious and specific manifestations of the infection will usually be present on admission or will develop soon after. <u>Thus, for the purposes of clinical diagnosis it is useful to focus on the less common but more specific clinical features of the severe spectrum of each of the etiologies of fever and rash. Milder presentations usually can not be differentiated clinically and resolve without treatment.</u>

Of the 5 above-mentioned categories of rash and fever, only viruses and bacterial exotoxin-mediated etiologies are pertinent in this case. Drug allergies aren't relevant in this child who was on no medication; the acute dominant symptom of sore throat makes spirochetal and rickettsial pathogens extremely unlikely, and the short duration of illness and lack of multi-system involvement makes it premature to entertain systemic auto-immune diseases on presentation.

a) <u>Viruses</u>: Africa is home to many viruses that cause rash and fever…
- Measles: with prodrome of fever, coryza, cough, conjunctivitis followed on the second day by the appearance of whitish Koplick spots on buccal mucosa, then followed by a maculo-papular rash on day 4 starting on the forehead and extending over the trunk over 4 days. While measles is considered a harmless nuisance in healthy children, it is often the final blow in malnourished children and a very common cause of mortality in unvaccinated kids in rural Africa or in refugee camps where it spreads rapidly. Superinfecting pneumonia is the usual cause of death.
- Rubella: "german measles" with fever, coryza, lymphadenopathy, arthralgias and a mild rash that extends from face to trunk. Milder than measles and associated with low morbidity/mortality, rubella causes congenital defects in the newborn if acquired during pregnancy.

- Parvovirus B19: Erythema infectiosum, ("fifth disease", "slapped face") is also associated in young adults with arthralgias/arthritis, and in patients with chronic hemolytic anemias such as sickle cell, an aplastic crisis.
- Enterovirus, Coxsackie or Echo viruses present with fever and rash that extends from face to trunk.
- Dengue: Dengue is transmitted by A.Aegypti that also carries Yellow Fever. Although there have been outbreaks of dengue in neighboring Kenya and cases reported throughout East Africa, the prevalence of dengue is unknown in Uganda due to inadequate surveillance and lack of diagnostic serology. Dengue presents with usually-severe myalgias and high fevers for 2-5 days with a transient macular rash seen in ~50% (of whites) that begins on the nape of the neck and extends to the face and trunk, lasting about 5 days and then desquamating. Dry cough, lymphadenopathy, and conjunctival suffusion may be seen. In its severe form, hemorrhagic complications and capillary leak with shock can be seen ("dengue hemorrhagic fever", in <1-2% of cases).
- Viral Hemorrhagic Fevers (VHF). The 4 VHFs to think about in East Africa (besides Dengue) that can cause rash/hyperemia and fever are from the families of Filovirus and Bunyavirus. (Two other VHFs, Lassa fever and Yellow Fever, are not among them: Lassa commonly manifests a petechial rash but is prevalent in West Africa, and Yellow Fever presents as a febrile syndrome with hepato-renal involvement in severe cases, but rash is rare.)

- *Filoviruses, Ebola and Marburg are potentially lethal RNA viral infections that are transmitted person- to-person via body secretions such as sweat, urine and vomitus, and occur in epidemics. They are associated with a 20-70% mortality rate in patients that come to medical attention. Patients present with sudden fever, headache, myalgias, nausea/vomiting/diarrhea, cough, conjunctival suffusion and a transient rash. The rash is truncal, maculo-papular, and desquamates on days 5-7 of illness. Fatalities occur between days 6-16 of illness from shock and/or diffuse bleeding which usually originates in the GI tract and is followed by bleeding in the oropharynx, lung, skin, and gingiva. Proteinuria, thrombocytopenia, and increased INR are seen in severe disease.*
- *Bunyaviruses, Crimean-Congo HF and Rift Valley Fever are both zoonoses transmitted by mosquitos, present with acute fever and diverse combinations of myalgia, neck pain, backache, headache, photophobia, sore throat, nausea/vomiting, diarrhea and abdominal pain. Confusion and aggressive behavior over the next few days can be followed by lassitude and depression. Abdominal pain may localize to the right upper quadrant with hepatomegaly and possibly jaundice. Conjunctival suffusion is seen in 50% and dermal hyperemia may be followed by bleeding from skin and mucosa. CCHF leads to death in the second week of illness in 20-30% of clinical cases, far more frequently than RVF (~1-2%). Recovery begins around day 10 of illness.*

- West Nile Virus: Clinical disease presents with acute fever, nausea, vomiting, headache, myalgias and in 20% (of whites) a diffuse morbilliform rash on the trunk, arms and legs. However, up to 80% of infected individuals have no symptoms; at the other extreme 1% develop the severe neurologic complications of seizures, ataxia, myelitis, and/or flaccid paralysis.
- HIV: Primary infection with HIV causes a non-pruritic, macular rash in 40-80% of patients 2-6 weeks post-exposure. Lesions are asymmetrically distributed, small erythematous macules on the trunk and arms, possibly involving the palms and soles, with an oral enanthem and pharyngitis ranging from erythema to ulceration. At this early stage, serology may be negative and plasma viral load necessary for diagnosis.

b) <u>Bacterial exotoxins</u>: Staphylococcus aureus and Streptococcus pyogenes cause several toxic exanthems.
- Toxic Shock Syndrome (TSS). Both Staph and Strep can cause TSS, which lasts between 10-20 days. The CDC criteria for TSS are fever>38.9C (102F), hypotension (BP<90mm Hg), rash – a diffuse macular erythroderm or scarlatiniform eruption with flexural accentuation, desquamation of palms and soles (after 1-2 weeks of illness), involvement of 3 organ system, and exclusion of other possible pathogens. Also frequently seen in TSS are strawberry tongue, conjunctival injection, edema of palms and soles, and loss of hair and nails. Most cases of Staph TSS nowadays are complications of post-op infections (which

can be symptomatically silent), HIV infection, URIs such as influenza and sinusitis, cellulitis or dermatitis. With supportive care, mortality in Staph TSS is 5%.

Strep TSS affects young adults under 50 years old who have overt soft-tissue infections or trauma. Localized pain and edema in an extremity progresses over 48-72 hours manifesting both local and systemic signs of TSS. Cellulitis often progresses to necrotizing fasciitis, myositis, and gangrene. Mortality rates in Strep TSS are more than 5 times higher than Staph TSS.

- Recalcitrant, erythematous, desquamating (RED) disorder: Due to a Staph exotoxin and described only in patients with AIDS, RED, like TSS, presents with fever and hypotension, diffuse macular erythema, ocular and oral mucosal injection, strawberry tongue and delayed desquamation. However, it is less fulminant than TSS - a much more prolonged illness (mean duration 50 days vs. 10-20 in TSS) with frequent recurrences. Mortality rates are high due to underlying HIV.

- Scarlet Fever (see below)

- Arcanobacterium (Cornebacterium) Hemolyticum: Perhaps as common as Scarlet Fever in children, and particularly so in adolescents and young adults in the West, Arcanobacterium haemolyticum (AH) causes pharyngitis, fever, lymphadenopathy, and/or maculopapular/scarlatiniform rash. AH is a gram-positive rod that appears to be more susceptible to erythromycin than to penicillin and has been isolated in 2.5-10% of cultured exudative pharyngitis, primarily in patients who are 15 to 18 years of age. The rash, which can be pruritic is caused by an exotoxin. It is typically seen first over the extensor surfaces before spreading centrally and usually spares the face. Its prevalence in Africa is unknown.

- Kawasaki Disease: a multi-system illness of infants and young children under 5 years with a peak incidence between 12 and 24 months. Its etiology is unknown, but an infectious etiology is suspected. KD is defined by fever of at least 5 days' duration plus at least 4 of the 5 following signs or symptoms:

- *Peripheral extremity changes (e.g. edema, erythema, desquamation)*
- *Polymorphous exanthema, i.e. multiple forms which in 2/3 manifests as perineal erythema*
- *Bilateral conjunctival injection without exudate*
- *Changes of lips and oral cavity (eg, erythema, strawberry tongue)*
- *Acute, nonpurulent cervical lymphadenopathy in 25%*

<u>Scarlet Fever</u>:

Scarlet Fever (SF) is the most likely diagnosis in this patient. SF is due to strep pyogenes exotoxins (SPE) produced by the gram + cocci in patients with pharyngitis. In the past it was associated with a mortality of around 25% due to the elaboration of a virulent exotoxin, SPE-A. Patients would succumb with presentations designated as either "toxic" - marked fever up to 107, delirium and uncontrolled convulsions - or "septic" - local invasion by strep into the soft tissues of the neck with upper airway obstruction, invasive otitis media, or bronchopneumonia. Currently, the less virulent SPE-B and C are responsible for most cases of SF, and mortality is rare.

SF is predominantly a disease of children less than 10 years old, and cases in adults older than 30 years are rare. SPEs elicit the cutaneous manifestations of SF by enhancing delayed-type hypersensitivity to streptococcal antigens, thereby requiring previous exposure for disease expression. Clinical findings include abrupt onset of sore throat, fever and headache, often with vomiting. Cervical lymphadenopathy is often followed by generalized lymphadenopathy. Without treatment fever usually lyses by day 7.

The exanthema appears early, spreads from neck to chest to extremities, and appears as a finely papular "sandpaper" rash on the trunk and extremities characterized, on closer inspection, by tiny elevated "papillae" that initially blanch, surrounded by erythematous areolae at the bases which can coalesce to form a confluent rash. It is most marked on the lower abdomen and inner thighs and in flexural locations such as the ante-cubital fossae, the axilla and the inuinal region. The rash is best appreciated by shining a light from the side, not overhead. Palms and soles can appear erythematous and swollen. Fragile capillaries bleed in flexural locations forming linear petechial streaks called Pastia's lines; Rumpell-Leede's sign refers to petechiae that appear beneath a tourniquet. The face is relatively

spared but "flushed" in appearance with circumoral pallor frequently seen. The red rash, which in Blacks can assume a purplish hue, lasts about a week.

Desquamation occurs in proportion to the intensity of the rash. It begins on the face (fine flakes) and neck at the end of the first week and spreads to the extremities, appearing early in the anal region and perineum. At the end of the second week, linear breaks are seen at the edges of the nails, and the palms and soles desquamate during convalescence between weeks 3-5, sometimes in thick sheets.

The mucous membranes are involved as well (enanthema). Most characteristic of SF is the "strawberry tongue" which evolves through 4 stages: day 1, heavy white coating of epithelial cells; day 2, red papillae appear atop the white coating; day 3, the coating begins to desquamate from the tip and sides to the back leaving a deeply red surface exposed; 4th day on, red papillae are visible on a red denuded surface ("raspberry tongue"), which gradually disappears between days 7-10.

This young patient had a classic presentation of an acute sore throat, headache, fever and vomiting with delirium and high fever - a moderate to severe form of SF. On exam, he had an exudative tonsillitis with Pastia's sign in the flexural creases, hyperemia around the buttucks, edema of the palms and soles, and strawberry tongue. He was not hypotensive, had no evidence of soft tissue infection and manifested no other specific signs of alternative (viral) diagnoses.

4. What frequent mistake do clinicians make in diagnosing the cause of fever in patients who have been previously treated for *gapfura* with crude tonsillectomy?

Clinicians are frequently distracted by the seemingly barbaric procedure of crude tonsillectomy, and attribute the fever and illness to exceedingly rare complications of the "operation" such as septic thrombophlebitis, septicemia induced by the trauma, etc. In doing so, they ignore the preceding illness that drove the patient and family to receive the tonsillectomy in the first place, the etiology of the persistent illness.

5. What is the appropriate treatment for this patient?

The appropriate treatment for SF is prompt antibiotics which halts the progression of the disease within 24-48 hours. First-line treatment is with penicillin; erythromycin or cephalosporins are also effective in patients with penicillin allergies.

6. If your diagnosis is correct, what other dermatologic manifestation will evolve over time? In what other diseases is this later skin manifestation seen?

Desquamation will evolve over time in most patients with SF, particularly severe SF. The usual sequence of desquamation is described above in # 3.

Other diseases manifest desquamation:
- Dengue
- Viral Hemorrhagic Fevers such as Ebola, Marburg
- Other Staph and Strep exotoxin-mediated diseases (see above) such as TSS
- Arcanobacterum Hemolyticum
- Kawasaki Disease
- Toxic Epidermal Necrolysis/Stevens-Johnson syndrome.. an immune reaction to herpes viral infections and drugs most commonly.

Suggested Readings:

Lupi, O., Tyring, S. Tropical Dermatology: Viral tropical diseases J Am Acad Dermatol 2003;49:979-1000

Velez, NF, Saavedra-Lauzon, A. Toxic Exanthems in the Adult Population The American Journal of Medicine (2010) 123, 296-303

Bialecki, C., Feder, H.M., The six classic childhood exanthems: A review and update J Am Acad Dermatol 1989; 21:891-903

Stevenson, F.E., Scarlet Fever The American Journal of Nursing 1941, 41(2): 131-144

UpToDate 2012 Fever and Rash in the Immunocompetent Host Lopez, F.A. et.al