Fever, eschar, and rash in a 4-year-old male

Matthew Christian Metzger, MD

The Herman and Walter Samuelson Children's Hospital

Baltimore, Maryland

The case

You are called to the emergency department (ED) to evaluate a 4-year-old boy with a fever consistently over 38°C and headache that began 7 days ago. On the third day of the illness, he showed his mother what appeared to be 2 insect bites on his left inner thigh and yesterday he developed a diffuse rash. He has been seen in his pediatrician's office and various EDs daily for the preceding 5 days.

When he initially presented to an ED on day 3 of the illness, he had a fever of 39°C, but otherwise appeared well. His fever was thought to be due to a viral illness unrelated to the erythematous papules on his thigh. The following morning, he woke up with severe leg pain and mild abdominal pain. He presented to another ED, where the papules were noted to have darkened, with tenderness of the abdomen and left calf. Again, his fever was felt to be due to a viral illness unrelated to presumed spider bites and supportive care and follow up with his pediatrician were recommended.

He was again febrile in his pediatrician's office the following day, where he complained of 8/\ out of 10 pain at the site of his lesions, difficulty walking, decreased appetite, and an ongoing headache. Examination revealed tender, mobile left inguinal lymphadenopathy and the lesions (Figure 1) were described as 2 tender papules with blue-black discoloration surrounded by a thin erythematous ring. He was prescribed cephalexin and mupirocin ointment as the bites were thought to be infected.

After his third dose, he remained febrile and was referred back to the ED. Now on day 6 of his illness, he remained well appearing and well hydrated despite a decreased appetite and energy level. His complete metabolic panel and blood count were notable only for a mild transaminitis and mild leukopenia. Although his sedimentation rate was within normal limits, his c-reactive protein (CRP) was elevated. An ultrasound of the lesions showed no evidence of an abscess or drainable fluid collection. Blood cultures were obtained. After discussion with both his pediatrician and a dermatology consultant, he was switched to clindamycin to add coverage for methicillin-resistant *Staphylococcus aureus* and advised to follow up as needed.

The following day, he presented to another ED having developed a new diffuse and mildly pruritic rash composed of erythematous papules that started on his face and then spread to include his trunk, back, arms, legs, and buttocks with sparing of the palms, soles, intertriginous spaces, and genitalia felt to be most consistent with a viral exanthem. The lesions were swabbed for herpes simplex virus (HSV) and he was discharged home to continue his antibiotics and supportive care.

He has now returned to the ED where he remains febrile with a headache, the initial 2 lesions on his thigh, and this new diffuse rash. He continues to drink well, but is eating only snacks and refusing to walk more than a few steps before asking to be held. Regarding the possibility of insect bites, his mother reports that the family lives in an old row home in Baltimore, Maryland. No one else in the family, including his older sister with whom he shares a bed, has similar bites or other symptoms. They have not noted any insects including bed bugs despite thoroughly searching and cleaning, but she has seen many stray cats and reports that their building and the surrounding area is infested with mice. The family has no pets and her son does not attend school or daycare.

His review of systems is otherwise negative, and his medical history includes only intermittent asthma. He takes no medications regularly; has no known allergies to drugs or otherwise; is appropriately immunized; and has never been hospitalized or undergone surgery. There is no family history of recurrent skin infections or abscesses.

Upon examination, he appears tired, but non-toxic and well hydrated. He has 2 1-cm punched out deep ulcers with necrotic central crusts on his left inner thigh and a diffuse rash composed of 40-50 discrete 2mm papulovesicles, all in the same stage of development and some of which have minute central pinpoint dry grey-black crusts. Repeat labs show mild hyponatremia, transaminitis with enzymes below 200, a mild leukopenia with elevated bands, thrombocytopenia, an elevated CRP and sedimentation rate, and an unremarkable urinalysis and creatinine kinase. His blood cultures are negative

at more than 48 hours. Lyme titers are collected and he is admitted to the floor for evaluation by dermatology.

Differential Diagnosis:

The differential for a previously healthy preschool age patient presenting with fever, headache, myalgias, and malaise includes numerous infectious etiologies, primarily viral and bacterial, that varies based on geography and epidemiology as well as some non-infectious causes of systemic inflammation such as rheumatological diseases and Kawasaki disease (KD). The diffuse papulovesicular rash present in this patient could be a viral exanthem, so the differential includes multiple viruses, particularly those in the herpes family like varicella-zoster and HSV. The initial skin lesions with localized erythema and pain are suggestive of a bacterial infection, such as cellulitis or an abscess. An eschar is a relatively rare and significant finding with its own differential that includes many febrile illnesses.[1] These do include spider bites as was initially suspected, however, that would not explain all his symptoms and the presentation seems too mild to represent necrotizing fasciitis or sepsis. Eschars with fever also occur in a variety of less common infections such as anthrax, tularemia, scrub typhus, and some rickettsioses.

Patient diagnosis, treatment, and course

The following morning, the patient was evaluated by dermatology, who felt his presentation was most consistent with rickettsialpox, an infection with *Rickettsia akari* transmitted from common house mice to humans by hematophagous mites, reasoning that no other "diagnosis fits the clinical picture any better than this. A *Staphyloccoccus* infection would not give a week of high fevers without significant purulence, cellulitis, etc. Although I can't exclude an atypical presentation of a viral infection, I cannot name any particular virus that would give this constellation of signs and symptoms. Lesions are not herpetiform in arrangement, itchy like chicken pox, or painful like HSV or zoster." The patient was treated with doxycycline, defervesced within hours of the first dose, and recovered without complications. Rocky Mountain Spotted Fever (RMSF) immunoglobulin G (IgG) and immunoglobulin M collected in the hospital

were negative, but when they were rechecked 2 months later, his RMSF IgG was positive at a dilution of 1:256 confirming the diagnosis of rickettsialpox.

Remarkably, 2 years later and despite moving to a new row home in a different neighborhood of Baltimore, Maryland, the patient presented to his pediatrician's office with an eschar on his left arm (Figure 2) and a 3-day history of headache and fatigue. RMSF serologies at that time were negative. A blood sample was sent to the Centers for Disease Control and Prevention (CDC) Rickettsial Zoonoses Branch for testing. Although his RMSF IgG was again negative, his *R. akari* IgG was positive at a dilution of 1:256 confirming a repeat infection. He was treated with a short course of doxycycline resulting in rapid resolution of his symptoms.

Discussion

Rickettsia is a genus of small, obligately intracellular, gram-negative bacilli transmitted to humans via hematophagous arthropod vectors such as ticks, lice, mites, and fleas.[2] Once inoculated into the skin, the microbe is phagocytized by dendritic cells and transmitted to local lymph nodes where they replicate. Infections then enter the bloodstream and disseminate to infect the endothelium of the microcirculation and endothelial damage ensues.[3] Pathogenic species are found throughout the world. Infections generally present with an undifferentiated febrile illness with headache and myalgias often accompanied by a rash and an eschar. Infections are difficult to distinguish from other acute febrile infections and rapid diagnostic testing is unavailable, but early diagnosis is essential as proper treatment results in quick alleviation of symptoms while delay in treatment is associated with poor outcomes and death.[2,4]

Rickettsia species are divided into 4 groups/clades: the basal ancestral group that does not cause human disease; the spotted fever group (SFG); the typhus group; and the transitional group so named for having characteristics between the spotted fever and typhus group.[5] Aside from the basal ancestral group, each contain multiple pathogenic species transmitted by 1 or more hematophagous vector. These

diseases are often named for the region in which they were discovered, but it should be noted that these names often fail to capture their actual geographic distribution.[2]

SFG rickettsioses are tick-borne and include at least 15 pathogenic species that vary from severely pathogenic with high case fatality rates to mild/asymptomatic infections. The namesake of this group and most pathogenic of all rickettsia species is *Rickettsia rickettsii*, which causes RMSF. Prominent symptoms of SFG rickettsioses include fever, headache, and myalgia. Gastrointestinal symptoms occur frequently and include nausea, vomiting, and abdominal pain. Rashes, such as the petechial rash of RMSF are common, especially in severe diseases, and an inoculation eschar or tache noire is typical of the group but very rare in RMSF2.[2]

The typhus group rickettsioses include louse-borne epidemic typhus and murine typhus (endemic typhus). The constitutional and gastrointestinal symptoms are the same as the SFG, but a maculopapular rash that spreads from the trunk outward has a variable incidence whereas eschars are atypical.

Epidemic typhus is caused by *Rickettsia prowazekii* present in the feces of infected body lice. Epidemics occur in unhygienic conditions such as war, natural disasters, or famine that promote the mass migration of people, crowding, and inability to change or launder clothing.[6] The lice live in the clothes and become infected when they feed on a rickettsemic patient. The lice, which are not adapted to increased body temperatures, flee symptomatic hosts and spread infection. They similarly flee dying patients. Some of those who recover remain latently infected and when conditions leave louse infestations unchecked, a single case off recrudescent typhus can start an epidemic.[2] Although rare today, epidemic typhus has played a major role throughout history with periodic epidemics as recently as the early 20th century and single epidemics killing millions. For instance, it is thought that a typhus epidemic initially acquired from Polish peasants killed more of Napoleon's Grand Army than enemy soldiers during his failed conquest of Russia. [6,7,8]

The second agent of the typhus group rickettsioses, *Rickettsia typhi*, is transmitted in the feces of the rat flea and causes murine typhus. It occurs at endemic levels throughout the world, especially in tropical and subtropical seaboard regions. Urban areas and port cities with heavy shipping traffic are often rife with rats, the primary reservoir. In the United States, peak incidence occurred in 1944 with 5041 cases nationally, but the use of insecticide dichlorodiphenyltrichloroethane on rat harborages during the mid-1940's resulted in a dramatic decline in cases to fewer than 100 per year within a decade. It remains endemic in Southern California and Texas. Severe illness is rare with most people recovering completely.[2]

The final clade of rickettsioses is the transitional group, which has 3 pathogenic species including the causative agent of rickettsialpox. Rickettsialpox was first identified following an outbreak in Regency Park, Queens, New York, in 1946 and was so named because the rash was initially felt to resemble chickenpox. Charles Pomerantz an exterminator and amateur entomologist investigated the building and identified the colorless mite *Liponyssoides sanguineus*, which is found on mice, as the vector of this new disease. Occurring primarily in urban areas due the high density of mice, mites, and humans, it remains endemic to New York City, New York.[9,10] Its distribution is difficult to assess due to the very low prevalence of confirmed cases, likely a result of a lack of awareness by medical providers and the lack of rapid diagnostic testing. Domestic cases have occurred primarily in major cities of the Northeast and Midwest United States. Several reports suggest this disease is much more common than previously thought with serologic evidence of exposure found in 16% and 9% of intravenous (IV) drug users in inner-city Baltimore, Maryland, where our case occurred, and Harlem in New York City, New York, respectively.[11] Internationally, rickettsialpox has been described in numerous countries including South Africa, Costa Rica, France, Italy, Turkey, Croatia, Ukraine, Russia, the Netherlands, Mexico, and South Korea.[12]

Rickettsialpox presents with a classic triad of fever, eschar, and rash. Seven to 10 days after the painless bite, a papular skin lesion appears at the bite location, becomes vesicular with a surrounding area

of erythema, and ruptures to form the eschar that is almost always present at the time of diagnosis. About 3 to 7 days after this initial lesion appears, patients develop constitutional symptoms and a sparse generalized and sometimes pruritic rash that begins as papules scattered on the face, trunk, and extremities without a particular sequence of involvement that subsequently vesiculate. The rash generally lasts a week and forms scabs that do not leave scars. Lab findings commonly include leukopenia and thrombocytopenia.[12]

Rickettsialpox is usually a self-limited disease with an excellent prognosis and no known fatalities, but treatment expedites resolution with clinical improvement often occurring during the first day of therapy. Diagnosis and treatment decisions are based on compatible clinical symptoms, knowledge of the epidemiology, and a thorough history including potential exposures. Although immunohistochemical and PCR-based detection of specimens can confirm acute infections, these are generally unavailable. The mainstay of diagnosis is serology using immunofluorescence assays. Serologies are commonly available for RMSF and *R. typhi*, but cross-reactivity allows these assays to identify any rickettsia infection. A positive titer during an acute infection is suggestive, but seroconversion or a greater than 4-fold increase in titer from the acute to the convalescent phase sera confirms the diagnosis.[2]

As demonstrated by this case, effective treatment requires the clinician to consider and accurately diagnosis rickettsialpox because many of the antibiotics frequently prescribed for the more common etiologies, such as cellulitis, that will be on their differential have no effect on *Rickettsia* including penicillins, cephalosporins, and sulfonamides. The first-choice treatment for all rickettsioses is oral or IV doxycycline dosed at 2.2 mg/kg to a maximum of 100 mg daily for a minimum of 5 days and continued for at least 3 days after defervescence.[2] Contrary to the widespread reluctance to use tetracyclines in children, there is ample evidence demonstrating the efficacy and safety of short and infrequent courses, particularly of doxycycline. This use does not result in the appreciable staining of developing permanent teeth.[13] Chloramphenicol is an effective second-line agent. Although oral macrolides and

fluoroquinolones are active against *Rickettsia*, fluoroquinolones are not recommended, and macrolides should only be used as an alternative in less severe rickettsioses. There are no vaccines for rickettsioses, so prevention relies on avoidance and control of the vectors and reservoirs, which in the case of rickettsialpox means control the mouse population.

Key Points

Rickettsialpox is an underrecognized infection transmitted from the common mouse by a tiny colorless mite that is likely endemic to many urban areas in the United States where patients and mice are in close proximity. It classically presents with a triad of fever, eschar, and rash often with headache, malaise, and myalgia. Although generally self-limiting, treatment results in rapid resolution and should be initiated when any rickettsial illness, rickettsialpox included, is suspected. Many commonly prescribed antibiotics, including penicillins, cephalosporins, and sulfonamides are ineffective. Patients should instead be treated with doxycycline, which has been shown to be safe for children in short, infrequent courses.

References

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