The Brief Case: Rat Bite Fever from a Kiss

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CASE

A 20-year-old otherwise healthy male presented to his primary care clinic with a 1-week history of fevers, rash, and polyarthralgias affecting his knees, elbows, and wrists that began 5 days following an acute diarrheal illness. In the clinic he was febrile to 38.5°C with a petechial rash initially on the palms and soles, which then spread to his trunk. The examination was also notable for cervical lymphadenopathy, two tongue ulcerations with clean bases, and the absence of joint effusion. Testing for influenza virus was negative, and the patient was sent home with a preliminary diagnosis of a nonspecific viral illness.

Subsequently, the patient's malaise and migratory arthralgias worsened, resulting in ambulation difficulties, and so he presented to the Emergency Department. He continued to complain of low-grade fevers and rash with intermittent headache and mild dysuria. He reported a monogamous heterosexual relationship, but he denied abnormal urethral discharge, genital lesions, intravenous drug use, tick exposure, or recent travel outside his Midwestern home state. The exam was notable for a whole-body diffuse petechial rash (Fig. 1) but negative for joint effusions or stigmata of endocarditis. Laboratory analysis revealed mildly elevated white blood cells at 11.5×10^9 /liter (normal range, 3.4×10^9 to 9.6×10^9 /liter) with neutrophilia, hemoglobin at 13.0 g/dl (normal range, 13.2 to 16.6 g/dl), and a C-reactive protein level of 79.1 mg/liter (normal range, 3.0 to 8.0 mg/liter). Hepatic enzyme testing, blood chemistry panel, urinalysis, and urine Gram stain were unremarkable. Given his history and lack of overseas travel, the differential for his illness included enterovirus, parvovirus, viral hepatitis, sexually transmitted infection, reactive arthritis, rheumatic disease, and bacteremia. Influenza and tick-borne illness were additional considerations, although the patient presented during the winter months, making influenza more likely than tick-borne illness. However, given a negative outpatient influenza result and the endemic nature of local tick-borne illnesses, a tick-borne panel was obtained that included testing for Lyme disease, *Anaplasma phagocytophilum*, *Ehrlichia chaffeensis*, and *Babesia microti*. In addition, blood cultures, urine studies for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and a multiplex molecular stool panel for gastrointestinal pathogens (BioFire, Salt Lake City, UT) were performed, and blood for hepatitis, HIV, and syphilis serologies was obtained. Given the absence of joint effusions, no diagnostic joint aspiration was performed. The patient received a single dose of ceftriaxone to cover for sexually transmitted infections before being admitted.

The patient received analgesia with naproxen and reported rapid improvement in his arthralgias. Overnight, blood cultures turned positive for Gram-negative rods in four

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For answers to the self-assessment questions and take-home points, see <https://doi.org/10.1128/JCM.00678-19> in this issue.

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FIG 1 Diffuse petechial rash of the extremities involving the palms (shown) and soles.

of six bottles after 18 h (Fig. 2). All four aerobic Bactec Plus Aerobic/F bottles (Becton, Dickinson, and Company, Franklin Lakes, NJ) flagged positive after 18 to 19 h of incubation, while both anaerobic bottles remained negative. The remainder of his infectious work-up was negative. Piperacillin-tazobactam, 3.375 g every 6 h, was started empirically. Small, gray colonies were apparent on sheep blood agar subcultured from the blood culture bottle after 18 h of incubation in 5 to 10% CO₂ at 37°C. Growth was not observed on chocolate agar or eosin methylene blue agar. The organism was identified as *Streptobacillus moniliformis* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) with the MicroFlex LT Biotyper 3.0 software (Bruker) using an in-house custom library (Mayo Clinic custom Bruker database, v.2632). The patient denied any history of bites but kissed his pet rat daily. Subsequent blood cultures remained negative. No antimicrobial susceptibility testing was performed on the isolate. Antimicrobial therapy was switched to ceftriaxone, 2 g daily, and the patient was discharged with a peripherally inserted central catheter line to complete a 14-day course.

DISCUSSION

Streptobacillus moniliformis is a pleomorphic, fastidious, Gram-negative bacillus and etiologic agent of rat bite fever (RBF) in the United States (1). Causative agents of RBF in other areas of the world include *Spirillum minus* throughout Asia and *Streptobacillus notomys* in Japan (1, 2). *S. minus* is uncultivable, a distinguishing feature from *Streptobacillus* spp. The prevalence of RBF in the United States is unclear, since *S. moniliformis* infection is not a reportable disease and laboratory confirmation of the diagnosis can be challenging. There are approximately 20,000 to 40,000 rat bites annually in the United States, with a 2 to 10% risk of acquiring RBF, suggesting the disease often goes undiagnosed and is certainly underreported (1, 3).

S. moniliformis infection classically occurs following a rat bite and is more common among children, specifically those living in poverty, due to the increased exposure risk (1, 4). Nontraumatic transmission has been reported via mucous membranes, including

FIG 2 Gram stain of *S. moniliformis* from aerobic blood culture bottle, demonstrating thin, stacked Gram-negative rods (GNRs) (A) and colony growth demonstrating GNRs with bulbar swellings (B). Magnification, $\times 1,000$.

when pet owners kiss their rat, or with other close contact (5). Cases without clear bite or scratch exposure highlight the need for a thorough history before removing RBF from the differential. Asymptomatic carriage of *S. moniliformis* among rats is common, occurring frequently in wild rats (50 to 100%) and laboratory-reared rats (10 to 100%) (1). After exposure, symptoms commonly present within the first 7 days, beginning with a nonspecific flu-like illness that can include headache, fever, myalgia, fatigue, and emesis (1). Progression of the disease includes migratory polyarthralgias, including both large and small joints in $\geq 50\%$ of cases and a petechial, purpuric, or maculopapular rash beginning with the extremities and involving the palms and soles in up to 75% of patients (1, 6). Other pathogens may lead to rashes on the palms and soles but do not cause the particular constellation of symptoms seen with RBF. Examples include measles, toxic shock syndrome, coxsackievirus, rickettsiae, syphilis, meningococemia, and bacterial endocarditis. Thus, a rash starting on the palms and soles accompanied by joint aches and fever should prompt questioning for rat exposure history. If antimicrobial therapy is delayed or not administered, mortality is reported to be 7 to 13% (1). Severe complications, such as endocarditis, can increase the risk of death to 43% (7). Outbreaks of *S. moniliformis*, referred to as Haverhill fever, a febrile illness often accompanied by vomiting and headache, are associated with consumption of food or water contaminated with rat excrement (1).

Definitive diagnosis of RBF caused by *S. moniliformis* classically relies on isolation of

the organism from blood, synovial fluid, abscess fluid, or other sources (3). However, the fastidious nature of *S. moniliformis* can make its recovery a challenge. Sodium polyanethole sulfonate (SPS), a component of many modern blood culture bottle formulations, has been shown to inhibit the growth of *S. moniliformis* when comprising at least 0.0125% (wt/vol) of the blood bottle volume (8). For this reason, use of blood culture bottles lacking SPS, typically anaerobic bottles, has been recommended (1). Routine adult blood culture sets at our laboratory are comprised of two BD Bactec Plus Aerobic/F bottles and one BD Bactec Lytic/10 Anaerobic/F bottle, which contain 0.05% (wt/vol) and 0.035% (wt/vol) SPS, respectively. Two sets of blood cultures were drawn peripherally from this patient, and all aerobic bottles were positive. In another case of RBF bacteremia diagnosed by our laboratory 1 month prior, 4/4 aerobic bottles also flagged positive (38 to 44 h), with anaerobic bottles remaining negative. These cases, combined with other examples in the literature, highlight that while growth conditions may be suboptimal and time to detection may vary, recovery of *S. moniliformis* is possible in aerobic adult blood culture bottles under routine conditions despite the presence of SPS (9, 10). Pediatric BD Bactec Peds Plus/F (BD) blood culture bottles likely contain less SPS (0.02% [wt/vol]) than the nonpediatric bottles. Description of the type of blood bottle used in pediatric cases of *S. moniliformis* has often not been provided in the published literature; thus, success of recovery with pediatric blood culture bottles is unknown (10, 11).

Recovery of *S. moniliformis* can be achieved on media containing blood incubated in 5 to 10% CO₂ at 37°C (1, 3). Methods suggested in the literature to enhance recovery include plating to tryptic soy agar (e.g., Trypticase soy agar [BD]), brain heart infusion broth supplemented with 15 to 20% bovine or horse blood, or the addition of serum or ascitic fluid to routine media containing blood (1, 3, 12). Growth can take 48 to 72 h, appearing as small, gray, shiny, umbonate colonies or cell wall deficient L-forms with a “fried-egg” appearance (1, 10). In broth, culture growth is known to exhibit a “puff-ball” appearance (13). Gram stain from positive blood culture bottles display the characteristic long, thin, stacked or clumped, Gram-negative rods (Fig. 2A) (10). From colony growth, *S. moniliformis* can exhibit characteristic tangled chains with bulbar swellings (Fig. 2B) (1). Identification of *S. moniliformis* from culture can be accomplished via MALDI-TOF-MS or partial 16S rRNA gene sequencing (3, 10, 14). *S. moniliformis* is included in the Bruker RUO 7854 database, but not the U.S. Food and Drug Administration (FDA)-cleared version (Bruker). The organism is not part of the FDA or RUO databases for Vitek MS (bioMérieux). *S. moniliformis* is reportedly inert for rapid biochemicals, including oxidase, indole, catalase, and urease (1). It is not included in the organism databases of Vitek2 (bioMérieux), MicroScan (Beckman Coulter), Sensititre (Thermo Fisher Scientific), and API (bioMérieux).

Broad range bacterial 16S rRNA gene PCR and sequencing has been used to detect *S. moniliformis* direct from specimen, including epidural abscess fluid, explanted mechanical mitral valve, and vesicle fluid (4, 15, 16). Sensitivity of this approach is unknown and studies to compare molecular methods with culture from clinical specimens have not been performed. However, given the variable success of culture-based methods reported in the literature, molecular approaches are a reasonable option when diagnosis remains unclear.

Preferred treatment of RBF bacteremia includes intravenous penicillin G or ceftriaxone for 1 week (1). In uncomplicated cases of bacteremia with initial response to treatment after 1 week, patients can be transitioned to oral penicillin V for an additional week, completing 2 weeks of therapy (1). In patients with a history of anaphylactic penicillin allergy, a 14-day course of doxycycline has proven to be a successful alternative regimen (1, 17). In invasive infections, such as endocarditis, extended therapy of up to 4 weeks with intravenous penicillin G or ceftriaxone is recommended (1, 18). In cases of *S. moniliformis* endocarditis, penicillin G in combination with streptomycin or gentamicin has been recommended in a previous case report but has not been further studied (1, 18).

SELF-ASSESSMENT QUESTIONS

1. Which of the following is a known transmission modality for rat bite fever?
 - a. Aerosol transmission from a person infected with *S. moniliformis*
 - b. Mucous membrane contact with rat saliva, urine, or fecal matter
 - c. Skin contact with a person infected with *S. moniliformis*
 - d. Aerosol transmission from an asymptomatic rat carrying *S. moniliformis*
2. Which of the following would best support growth of *S. moniliformis*?
 - a. Eosin methylene blue agar incubated in 5 to 10% CO₂ at 37°C
 - b. Sheep blood agar incubated in room air at 30°C
 - c. Trypticase soy agar incubated in 5 to 10% CO₂ at 37°C
 - d. Hektoen enteric agar incubated in microaerophilic conditions at 37°C
3. What is the preferred initial treatment for bacteremia due to *S. moniliformis*?
 - a. Oral penicillin
 - b. Intravenous penicillin G
 - c. Oral doxycycline
 - d. Intravenous penicillin G with either streptomycin or gentamicin

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