

# Migratory Polyarthralgias and Skin Rash: Rat Bite Fever with a Positive Anti–Cyclic Citrullinated Peptide

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## Abstract

Rat bite fever is a rare, underdiagnosed disease caused by *Streptobacillus moniliformis* in the United States, and is typically characterized by leukocytosis, elevated C-reactive protein, migratory polyarthralgias, and pustular skin rash. Rat bite fever is frequently misdiagnosed as either a viral illness or a rheumatologic disease and carries a high mortality risk if untreated. We report the first case of rat bite fever associated with positive anti–cyclic citrullinated peptide. The patient initially presented with low back pain and developed a pustular rash as well as severe asymmetric polyarthralgias. Blood cultures turned positive for *S. moniliformis* and the patient completed a 4-week course of antibiotics for presumed septic arthritis.

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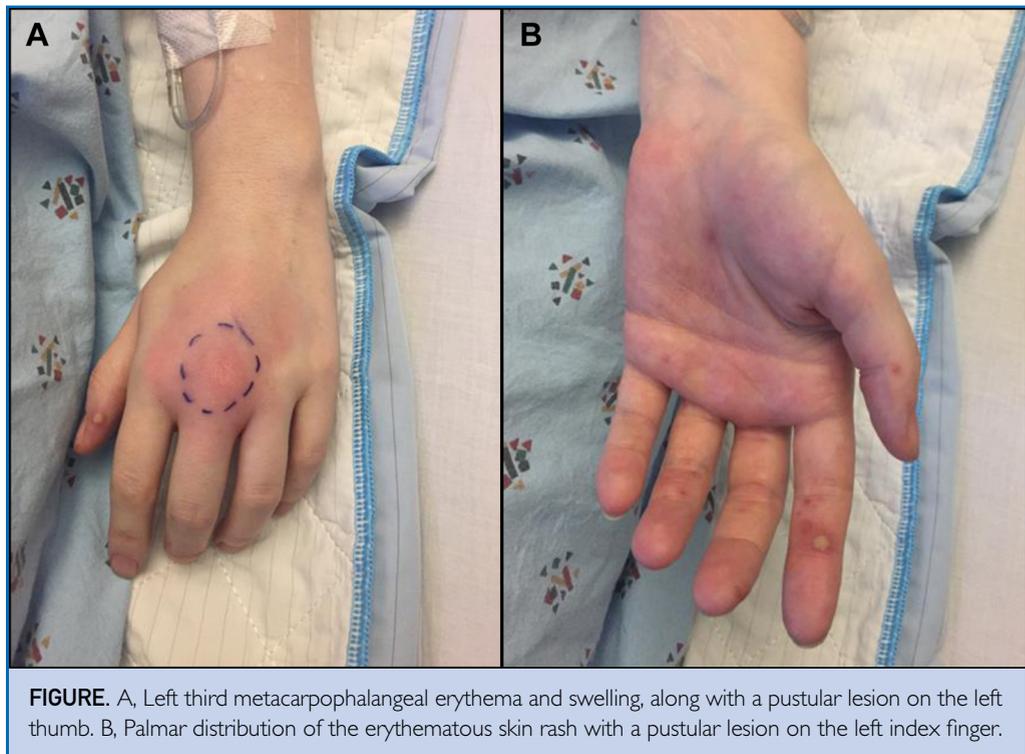
## CASE

A 27-year-old female with a history of depression and anxiety was admitted for evaluation of acute onset low back pain. She endorsed fevers, chills, nausea/vomiting, and generalized malaise 3 days before admission, with a documented fever of 39.6°C at home. She rated her lumbar pain 3 of 10 on a pain scale at rest and up to 10 of 10 with any movement, with radiation to her left leg, hip, and thigh. She denied trauma, bowel/bladder incontinence, intravenous drug use, or history of cancer. She had been sexually active with one male partner, always using condoms. Family history was significant for rheumatoid arthritis. On admission, workup revealed neutrophil-predominant leukocytosis with a white blood cell (WBC) count of  $14 \times 10^9/L$  ( $3.4 - 9.6 \times 10^9/L$ ), elevated C-reactive protein (CRP) of 277.8 mg/L ( $<8$  mg/L), and moderate blood/red blood cells on urinalysis. Computed tomography scan of the abdomen/pelvis was negative for nephrolithiasis. Computed tomography scan of the lumbar spine showed chronic lumbarization of S1, mild disc bulging at L5-S1, and no acute fractures. Her pain was managed with a multimodal regimen, and she continued to have elevated but fluctuating CRP and WBC values.

On hospital day 4, the patient developed asymmetric polyarthralgias involving the left third metacarpophalangeal joint, right wrist, right shoulder, and bilateral ankle joints. Additionally, the patient was noted to have an erythematous and pustular skin rash involving the palms (Figure).

Nucleic acid amplification tests from urine samples were negative for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Furthermore, fourth-generation combined human immunodeficiency virus (HIV) 1/2 immunoassay, syphilis immunoglobulin G (IgG) antibody, Parvovirus B19 serology, Epstein-Barr virus (EBV) IgM/IgG and EBV nuclear antigen antibody, and cytomegalovirus DNA testing were all negative. Rheumatoid factor (RF) was positive (20 IU/mL [ $<15$  IU/mL]) and anti–cyclic citrullinated peptide (anti-CCP) antibody testing was strongly positive at greater than 250 U ( $<20$  U). Plain films of bilateral wrists and left hand were negative for joint space narrowing or erosive arthritis. On further questioning, the patient reported that she owns three pet rats, and while trying to pull one of the rats from its cage, she was bit on her right thumb 2 days before the onset of symptoms. Rat bite fever (RBF) was suspected, blood cultures were drawn, and the patient was started empirically on 2 g of intravenous ceftriaxone

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daily. The microbiology laboratory was notified of organisms of suspicion. Arthrocentesis of the right wrist joint (22 hours post initiation of antibiotics) yielded purulent synovial fluid, although the procedure was terminated early because of discomfort. Synovial fluid gram stain was negative for organisms but showed numerous WBCs. However, synovial fluid cell count and bacterial cultures were not performed because of inadequate volume. The patient endorsed right ankle pain, with no evidence of effusion by ultrasound.

By hospital day 7, blood cultures showed growth of *Streptobacillus moniliformis* in 4/6 bottles, confirming RBF. Repeat blood cultures 2 days later were negative. Magnetic resonance imaging of the lumbar spine did not show evidence of discitis. The patient had significant improvement in her symptoms with resolution of leukocytosis and was discharged on hospital day 12 on 2 g of intravenous ceftriaxone for a total of 2 weeks followed by amoxicillin/clavulanate 875/125 mg twice daily for an additional 2 weeks. During outpatient follow-up 2 weeks after discharge, the patient endorsed near complete resolution of polyarthralgia and skin lesions, and additional testing/imaging was not performed.

## DISCUSSION

Patients presenting with fever, rash, and arthralgias have a broad differential diagnosis, including but not limited to, infectious (endocarditis, disseminated gonococcal arthritis, reactive arthritis, Parvovirus B19, secondary syphilis, or cytomegalovirus/EBV/HIV), rheumatologic (systemic lupus erythematosus, spondyloarthropathy, rheumatoid arthritis, or SAPHO syndrome), and other etiologies based on exposure history. In our patient, a broad laboratory workup was notable for only positive RF and anti-CCP antibodies before learning about the rat bite, highlighting the importance of a thorough exposure history when infectious etiologies are suspected.

RBF is a rare disorder most commonly caused by *S. moniliformis* in the United States, and by *Spirillum minus* in Asia (analogous disease named sodoku).<sup>1</sup> It was first reported in the United States in 1839, with only 200 documented cases.<sup>2</sup> Its incidence is largely underestimated due to frequent misdiagnoses, specialized techniques required to recover the microorganism from cultures, and lack of obligatory reporting of infections. Furthermore, nearly one-third of reported cases have no known bite exposure.<sup>1</sup> Rats are the predominant reservoir,

with 10% to 100% of pet rats and 50% to 100% of wild rats colonized by *S. moniliformis*.<sup>1</sup> Prior reports have documented transmission and/or colonization in guinea pigs, gerbils, ferrets, cats, and dogs, although data are lacking for the exact identification of the *Streptobacillus* species. For nearly 90 years, *S. moniliformis* was the only member of the *Streptobacillus* genus, until the recent discovery of *S. hongkongensis* and *S. felis*, which have been reported to cause septic arthritis in humans and pneumonia in cats, respectively,<sup>3</sup> and *S. notomytis* which was implicated in RBF in humans but was initially misidentified as *S. moniliformis*.<sup>4</sup> Importantly, there has been a striking increase in the number of owners of such exotic pets and wildlife which serve as sources of zoonotic infections.<sup>5</sup> The demographics of rat bites have changed from predominantly young children residing in poorer, crowded urban dwellings, to personnel in laboratories or pet stores and pet owners in homes.<sup>6</sup> Rat bites account for approximately 1% of animal bites, with the risk of *S. moniliformis* infection following a bite approximately 10%, significantly higher than that associated with a cat or dog bite.<sup>1</sup> Although it is unrealistic to suggest that all adults or children should wear gloves or protective clothing while handling pet rats, patients should seek prompt medical care for a rat bite. The American Academy of Pediatrics recommends antibiotic prophylaxis in selected patients for a rat bite.<sup>7</sup> Patients who develop rash, fever, arthralgia, or systemic symptoms should be seen promptly for early diagnosis and treatment of possible RBF.

As the causative organism of RBF, *S. moniliformis* is a highly pleomorphic, filamentous, non-motile, and non-acid-fast gram-negative rod that is typically arranged in chains and loose clusters. These bacteria grow slowly (can take up to 7 days), and are inhibited by the presence of sodium polyanethol sulfonate (SPS), an anticoagulant found in standard aerobic blood culture bottles.<sup>8</sup> Inhibition occurs at SPS concentrations as low as 0.0125%, whereas commercial aerobic blood culture bottles typically contain 0.05% SPS.<sup>8</sup> As such, laboratories need to be notified of potential *S. moniliformis* infection such that the organisms can be appropriately cultured in alternative aerobic (Trypticase soy agar or broth, resin bead) or anaerobic culture systems. As several new species of

*Streptobacillus* have been recently identified,<sup>3,4,9</sup> additional testing is typically performed to determine the exact species. Per discussions with the microbiology laboratory, the patient's isolated bacteria were analyzed using MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization coupled with Time of Flight Mass Spectrometry), and confirmed to be *S. moniliformis*.

RBF typically comprises of two phases — initial fever, fatigue, myalgias, nausea, vomiting, headache, and pharyngitis within several days of inoculation, followed by migratory asymmetric polyarthralgias (medium/large joints) and skin rash involving the palms and soles (maculopapular, pustular petechial, or purpuric) roughly 3 to 7 days later.<sup>1</sup> Laboratory evaluation commonly shows leukocytosis and markedly elevated CRP. Diagnosis is often clinical based on history of rat bite, with definitive diagnosis upon growth of *S. moniliformis* from blood or synovial fluid. The bacteria are sensitive to numerous antibiotics, although the preferred treatment is penicillin G (adult dose: 200,000 IU every 4 hours for 7 days, transitioning to oral penicillin to complete a 2-week course), or ceftriaxone (adult dose: 1 to 2 g every 24 hours) for 2 weeks. Complications include bacteremia, endocarditis, myocarditis, septic arthritis, pericardial effusion, pneumonia, meningitis, nephritis, discitis, multi-organ failure, and death (~10% mortality if untreated), with most complications requiring 4 to 6 weeks of antibiotics.<sup>1</sup> Recently, a case of critical limb ischemia has been reported.<sup>10</sup> Endocarditis carries a particularly high degree of mortality if untreated (~50%), with majority of deaths occurring within 2 to 3 weeks of initial exposure and in patients with pre-existing valvular disease.<sup>1,11</sup> In our case, endocarditis or pericarditis/pericardial effusion was not suspected due to quick clearance of bacteremia within 2 days, absence of any murmurs, pericardial rubs or muffled heart sounds on auscultation, and clinical improvement with treatment.

Importantly, the polyarthralgias seen in RBF are typically reactive arthritis without evidence of suppurative joint infection. Rat bite-associated septic arthritis has been reported in the absence of other RBF symptoms such as fever, rash, or bacteremia, highlighting the bacteria's predilection to synovial and serosal surfaces.<sup>12</sup> In these cases, arthrocentesis should

be performed to distinguish streptobacillary septic arthritis from reactive arthritis seen with RBF, especially in the presence of significant joint effusions and nonresolving arthralgias. Confirming the diagnosis of septic arthritis in cases with RBF can be challenging, as synovial fluid may appear purulent with an elevated WBC count, but up to 20% of cases are culture-negative.<sup>13</sup> Accordingly, our patient was found to have a suppurative arthritis of her right wrist, although volume of synovial fluid was inadequate for optimal culture, and no quantification of synovial WBCs was possible. In suspected septic arthritis cases with negative synovial fluid cultures, the diagnosis can be established using 16S ribosomal RNA (rRNA) polymerase chain reaction (PCR) amplification test from synovial fluid.<sup>13</sup> We did not perform 16S rRNA PCR testing on the synovial fluid sample as this would not have changed our management plan because she may have had a false-negative result due to synovial fluid collection occurring 22 hours after initiation of antibiotics. Her presenting back pain was presumed to be mechanical in nature given the lumbarization of S1 and unlikely to be related to RBF in the absence of discitis on magnetic resonance imaging. As such, due to presence of numerous WBCs in the synovial fluid of the wrist, the patient was treated for a 4-week total course of ceftriaxone followed by amoxicillin/clavulanate for presumed septic arthritis.

Given the inflammatory nature of RBF polyarthralgias and low specificity of RF, a number of RBF cases have been previously misdiagnosed as rheumatoid arthritis.<sup>1</sup> Although anti-CCP antibodies have reported specificities of 95% to 97% for rheumatoid arthritis,<sup>14</sup> they have been found to be positive in certain infections, including *Mycobacterium tuberculosis*, *Nontuberculosis mycobacterium*, hepatitis B virus/hepatitis C virus, leprosy, HIV, EBV, and Lyme disease.<sup>15,16</sup> Although our patient has a family history of rheumatoid arthritis, the absence of joint space narrowing or erosions on hand/wrist plain films coupled with the near complete resolution of her polyarthralgias following a course of antibiotics strongly argues against any concomitant rheumatoid arthritis. Additionally, the degree of anti-CCP elevation (>250 U) makes an actual false-positive (ie, insignificant result or lab error) exceedingly unlikely. No follow-up testing of anti-CCP or RF

has been performed to date given the lack of indication for testing. To our knowledge, this is the first case of RBF with positive anti-CCP antibodies. It is unclear whether anti-CCP positivity in this case is secondary to joint involvement by RBF infection or if it represents early/subclinical rheumatoid arthritis, as causality cannot be established with the current study design. Further studies are needed to establish the association between RBF arthropathy and anti-CCP positivity.

## CONCLUSION

RBF is a rare, underdiagnosed disease typically caused by *S. moniliformis* in the United States, frequently due to a rat bite or scratch. Clinical features of RBF include fever, fatigue, nausea/vomiting followed by migratory asymmetric polyarthralgias, and pustular skin rash. Laboratory evaluation commonly shows leukocytosis and elevated inflammatory markers. Confirming diagnosis of RBF is difficult, as *S. moniliformis* grows slowly and is inhibited by SPS present in standard aerobic culture bottles. As such, a high index of suspicion is required and laboratories must be notified of potential organism to enable optimal culture conditions, and may require additional techniques such as 16S rRNA PCR or MALDI-TOF MS to confirm exact species of *Streptobacillus*. Exotic pet owners and lab personnel should seek urgent treatment if they develop characteristic symptoms following a rat bite, as untreated RBF carries a high mortality rate (10% overall, 50% if endocarditis is present). Treatment of choice includes penicillin G or ceftriaxone. Importantly, despite the established high specificity of anti-CCP antibody for rheumatoid arthritis, clinicians should be aware of the increasing evidence for positive anti-CCP in the presence of various infectious diseases, possibly including RBF.

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**Abbreviations and Acronyms:** **Anti-CCP** = anti-cyclic citrullinated peptide; **CRP** = C-reactive protein; **RBF** = rat bite fever; **SPS** = sodium polyanethol sulfonate; **WBC** = white blood cell

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