CASE STUDY


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ABSTRACT

Rat bite fever is an under diagnosed, rare systemic illness, with 13 per cent mortality rate without treatment. It is caused by infection with Streptobacillus moniliformis, a gram-negative bacillus. Infection can result from a bite or scratch from an infected or colonized rat, or from handling rats at home or the workplace.

We describe a case of rat bite fever in a 46-year-old healthy lady, which was transmitted without a history of bite or scratch. With prompt liaison with local microbiologists we grew Streptobacillus moniliformis from both blood and synovial fluid for the first time. Our case was complicated by septic arthritis despite treatment with appropriate antibiotics.

Key Words
Rat bite fever, Streptobacillus moniliformis, septic arthritis

Implications for Practice:
1. What is known about this subject?
Rat bite fever is a zoonotic infection caused by Streptobacillus moniliformis. Delayed diagnosis and treatment may lead to a variety of potentially serious complications.1

2. What new information is offered in this case study?
We report a rare case of a rat bite fever, without any evidence of bites or scratches and developing complications despite treatment with antibiotics.

3. What are the implications for research, policy, or practice?
This case study highlights that RBF needs prompt treatment and should be kept in mind in an acute febrile illness in individuals with compatible history.

Background
Rat bite fever (RBF) is a rare febrile illness, mostly under-diagnosed, caused by infection with either Streptobacillus moniliformis or Spirillum minus, both gram-negative bacilli.2 S. moniliformis is commonly found in the nasal and oropharyngeal flora of rats. The rate of nasopharyngeal carriage of S. moniliformis by rats (even healthy laboratory rats) is quite variable, reportedly being as high as 100 percent.3,4

Infection with S. moniliformis can result from a bite or scratch from an infected or colonized rat, or from handling rats at home or the workplace (e.g., laboratories or pet stores). There is about 10 per cent risk of infection after a rat bite though approximately 30 per cent of patients with rat bite fever do not recall or report having been bitten or scratched.4,5 The incubation period for the infection with S. moniliformis is less than 7 days following exposure. Symptoms typically start with fever, nausea and vomiting, pharyngitis and headaches, migratory arthralgias and myalgias. By the time the patient present with symptoms after inoculation via a bite or scratch, the wound has usually resolved.2

Case details
A 46-year-old woman presented with a 2-day history of
arthralgia affecting her right shoulder, right ankle and left knee associated with malaise and pyrexia. She was a full time caregiver for her children, smoked 10 cigarettes a day and had done for 20 years, and had no other significant past medical history. There was no history of trauma. A few days prior to this, she had presented to the emergency department with gastroenteritis, being discharged home on the same day. Musculoskeletal examination revealed mild swelling around the right ankle lateral malleolus without any tenderness, skin redness or warmth. The patient had a good range of motion in all other joints. No skin abnormalities were present. The other systems examined normally, and observations were also normal.

A diagnosis of possible reactive arthritis was made, and she was admitted to hospital and commenced on prednisolone 50mg daily as well as simple analgesia. Initial blood tests included: white cell count of 4.5×10^9/L (neutrophils: 3.4×10^9/L), platelet count of 100×10^9/L (reference interval [RI], 150-400), erythrocyte sedimentation rate of 45mm/hr (reference interval [RI], 1-14), negative blood cultures, negative viral serology to Hepatitis B and C, HIV, Arbovirus, Barmah Forest, Rubella and Ross River Virus. Anti-cyclic citrullinated peptide, RF and ENA antibodies were all negative. ANA was positive (1:40, mitotic spindle pattern). Chest and ankle X-rays were normal.

Despite therapy with oral corticosteroids, after two days there was no clinical improvement. On the third admission day, the right shoulder and right ankle pain improved but the patient developed progressive worsening left shoulder pain and left knee swelling with no infective signs. Left knee and shoulder X-rays were unremarkable. No change in management was instituted. The arthralgia in the left knee and shoulder persisted over the next 2 days, and repeat investigations demonstrated an increased ESR of 114. The patient was transferred to a tertiary hospital for specialist rheumatology review, where the patient was offered admission for viral or atypical reactive arthritis; due to family commitments, the patient decided to return to our unit. Suggested management from the rheumatology team included further investigations including HLA B-27 testing as well as knee aspiration, whilst continuing prednisolone 50mg/day with a plan to taper the dose in four weeks. HLA B-27 was negative and knee joint aspirate was unremarkable.

On corticosteroids, the patient gradually improved, however on day seven, the left knee swelling worsened, still without redness or warmth, associated with systemic temperature of 37.7°C, rigors and malaise. The septic screen was repeated including another knee aspirate, but no antibiotics commenced. She had another episode of fever (38.0°C) the following morning associated with a generalised headache and blurred vision. On examination, she was tachycardic with mild hypotension. Additional blood cultures were taken and intravenous flucloxacillin and gentamicin commenced in combination with fluid resuscitation. She was transferred to the high dependency unit. A third knee aspirate subsequently revealed white blood cell count of 71,300 (Neutrophils 90 per cent), red blood cell count of 450, whilst a full blood count showed a white blood cell count of 25.7×10^9/L (reference interval [RI], 4-11), and C-reactive protein of 50mg/L (reference interval [RI], <5). CT abdomen, pelvis and trans-thoracic echocardiogram were normal. The patient refused Lumbar Puncture.

Despite being on antibiotics, there was no clinical improvement and the CRP rose to 166, without a clear diagnosis. Another detailed history was taken and revealed that she had a rabbit, dog and several pet rats at home and had close contacts with them. On the second week, the second knee aspirate and 1 set of blood cultures (taken during an episode of fever) grew gram-negative rods. After liaison with local microbiologist and on the basis of the history of animal exposure, specifically pet rats, and the blood culture results, a working diagnosis of “Rat bite fever” was made. The organism was oxidase and catalase negative and had a typical gram stain, thin long pointy which were enough for presumptive diagnosis of Rat bite fever. Hence, Antibiotic treatment was changed to intravenous penicillin (1.2g, six hourly) and the corticosteroids were ceased.

During the first three days after commencing penicillin, there was an initial clinical and biochemical improvement with the CRP falling to 56; however at the end of the second week, the left knee became swollen, red and tender. The CRP increased to 171 whilst an additional knee aspirate showed a WBC of 162,000 (Neutrophils 95 per cent) and a RBC of 22,000. Both knee aspirate and repeated blood cultures were negative. The patient was transferred for specialist orthopaedic input, and an arthroscopic knee washout was performed. Following intravenous penicillin for another 3 weeks, the patient was discharged on oral amoxicillin for 3 weeks. The initial working diagnosis was confirmed, when after 3 weeks, microbiological confirmation of growth of *Streptobacillus moniliformis* in both knee aspirate and blood was obtained. Initially, the organism was not identified using MALDI-TOF mass spectrometry. After Streptobacillus moniliformis was finally identified by 16S ribosomal RNA (rRNA) sequencing.
Isolation of Streptobacillus moniliformis from the synovial fluid was more challenging. The organism wasn’t inoculated directly from the standard media (agar and chocolate plates). However, synovial fluid was transferred into the blood culture bottles and following an extended incubation time, Streptobacillus moniliformis was isolated from the synovial fluid.

The patient was reviewed in outpatient clinic, there were no further complications and there was complete recovery.

Discussion
This case shows a diagnostic and management dilemma. The patient had presented with a relapsing-remitting systemic illness involving fever, malaise, and migratory polyarthralgias in combination with episodes of partial response to treatment. Notably, amongst several sets of blood cultures, just the one, which was taken with a mild fever (37.7°C), was positive. Without a high index of suspicion, repeated history taking and repeated cultures of blood and synovial fluid, the diagnosis may never have been established. There have been no reports identifying S. moniliformis from 2 different sites and though no history of being bitten or scratched was elicited through detailed interview, with a high level of clinical suspicion, we were able to identify the causative organism from blood and synovial fluid cultures for the first time. This case highlights the importance of fundamental clinical skills and processes specifically the importance of taking a thorough history including contact with animals and pets, and liaising with relevant specialists in a timely manner.

RBF is most commonly diagnosed empirically, as growing S. moniliformis is difficult and requires specific media (serum-supplemented agar) for isolation and must be incubated in a 5-10 per cent CO₂ environment. Specimens of blood, synovial fluid, or aspirates from abscesses should be inoculated into bacteriologic media without sodium polyanethol sulfonate (SPS), such as an anaerobic culture bottle. SPS is present in most aerobic blood culture media and it inhibits growth of the organism. The microbiology laboratory should be alerted so that specific media and culture conditions can be used to optimize isolation of the organism.8 Other laboratory investigations are most commonly non-specific, and may show a moderately elevated WBC and sedimentation rates.7 No serologic test is available; however, 16S ribosomal RNA gene sequencing can be used for diagnosis if there is a sufficiently high clinical suspicion and the facility is available.8,9

In patients with a compatible clinical presentation and exposure history, immediate empirical treatment is needed; since laboratory confirmation is difficult and may take several days and prompt therapy can prevent complications. Penicillin or ceftriaxone are the treatment of choice for RBF with total duration of 14 days of initially intravenous then oral antibiotics being adequate for uncomplicated disease, however this is based on expert opinion; no trials have been performed. A variety of complications of RBF have been reported, the most serious including meningitis,10 endocarditis,11,12 myocarditis, pneumonia,13 focal abscesses,14 bacteraemia, septic arthritis,15,16 and multi organ failure.1 The majority of these occurred in the absence of effective antimicrobial therapy.2 However, our case was complicated by septic arthritis despite being on antibiotics. In the case of a complicated clinical course, usually 4 weeks of intravenous penicillin or ceftriaxone is used, with further adjustments made based on the clinical progress and organ involvement.17

In our patients we concluded that S. moniliformis was likely transmitted without a bite or scratch, and this should kept in mind in individuals exposed to rats, including at home as pets, at work in pet stores and laboratories, and in occupations at risk such as water treatment workers. Preventing severe disease among people who have exposure to rats involves increasing their awareness of the signs and symptoms of RBF and in persons at risk, information regarding RBF should be provided to pass on to their clinician in the event of illness. Moreover, following a rat bite it is reasonable to administer a three-day course of oral penicillin V; however, the efficacy of antimicrobial prophylaxis is unknown.

Conclusion
This case report demonstrates a challenging case of RBF, with no history of bite or scratch and developing complication despite being on antibiotics. Rat bite fever is a rare but lethal infection if left untreated. It is most commonly diagnosed empirically because growing S. moniliformis is difficult. With high level of suspicion in a patient with a compatible history and exposure, blood cultures should be taken even in cases of mild fever and empirical treatment should be instituted early in order to prevent serious and potentially life threatening complications.

References

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The authors, Mahmoodi E, Erdstein A, Grainge C. declare that:
1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.