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Rethinking dogma: an Asian case report of streptobacillary rat-bite fever

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ABSTRACT

Rat-bite fever (RBF) is a rare but potentially fatal zoonotic disease that has resurfaced in literature from time to time. RBF has conventionally been attributed to *Streptobacillus moniliformis* in the Western World and *Spirillum minus* in Asia. However, numerous case reports of *Streptobacillus moniliformis* in Asia highlight the need to rethink this assertion. We encountered a patient with streptobacillary RBF and a history of recent travel to Bangladesh. We present the salient clinical features and processes in arriving at this diagnosis. The patient was successfully treated with no major sequelae, likely due to the early institution of appropriate antibiotics. We present our learning points on RBF including recognition, early and appropriate antibiotics and the challenges in diagnosing RBF.

1. Introduction

Rat-bite fever (RBF) is an uncommon zoonotic disease, conventionally attributed to *Streptobacillus moniliformis* (*S. moniliformis*) in North America/Europe and *Spirillum minus* in Asia[1]. The risk of RBF developing from a rat-bite is 10%, with a mortality rate of up to 13% if untreated[1,2]. In addition, RBF carries the potential sequelae of endocarditis and suppurative polyarthritis. Rarely, polyarteritis nodosa, pericardial effusion, erythrophagocytosis, meningitis, pneumonitis and osteomyelitis have also been described[1,3]. In recent years, clinicians have reported cases of RBF presenting with predominantly dermatological complaints as well[4-6]. RBF is likely under-recognized and under-reported in many developed countries and should be considered in the context of a suggestive history. However, *S. moniliformis* is a fastidious organism and infrequently isolated from cultures. Practitioners should start the appropriate antibiotics and seek an expert opinion immediately.

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2. Case report

A 44-year-old Bangladeshi man with a background of hypertension and hyperlipidemia was admitted to hospital with 3 days of fever, chills and rigors. He had a dry cough that began insidiously, generalized body ache and non-bilious or bloody vomiting. He had been bitten 5 d prior to presentation by a rat near his shop house, which was rat-infested. He also reported travelling back to Bangladesh in the previous 2 weeks without taken malaria prophylaxis or received any vaccinations. There, he had participated in fresh-water swimming and been in close contact with domestic animals such as dogs and cats. He was well when he returned from his travels. In addition, his son had been diagnosed with an upper respiratory tract infection just prior to our patient's admission. He had seen his family physician and the physician irrigated and dressed the wound, and prescribed topical antibiotic cream. No systemic antibiotics (oral or intravenous) had been administered prior to the patient's presentation at the hospital.

At presentation to the emergency department, he was dehydrated but not jaundiced. He was febrile and tachycardic but otherwise hemodynamically stable. No

cardiac or pulmonary abnormalities were detected on examination. He did not have any abdominal tenderness or organomegaly. Small submandibular lymph nodes were palpated. The bite on the right foot was subcentimeter and almost healed. No regional lymphadenopathy, joint swelling or tenderness was detected.

His white cell count was 20.9×10^9/L, with a neutrophil predominance of 89%. His absolute neutrophil count was 18.6×10^9/L. The procalcitonin level was 1.3 μg/L and the C-reactive protein 159 mg/L on admission. The renal panel showed hyponatremia (131 mmol/L), hypokalemia (2.6 mmol/L) and elevated creatinine (110 μmol/L). The liver panel showed mild transaminitis with total bilirubin 27 μmol/L, alkaline phosphatase 112 IU/L, alanine aminotransferase 68 IU/L, aspartate aminotransferase 54 IU/L. The chest X-ray was unremarkable.

Aggressive fluid resuscitation and electrolyte replacement was instituted. In view of the history of rat-bite, 4 megaunits of benzylpenicillin was given intravenous injection (IV) after the first set of blood cultures was taken. In consultation with infectious disease physicians, two more sets of blood cultures were repeated, in addition to blood films for malaria parasites and serology for *Leptospira*, *Orientia* and *Rickettsia* spp. As their advice, the patient was started on IV ceftriaxone 1.5 g and oral doxycycline 100 mg every 12 h. Two days after admission, the primary team was alerted by laboratory staff to the growth of Gram-negative bacilli in the first set of blood cultures. Upon subculture to specific solid media, the organism exhibited visible growth after 24 h of incubation. However, the growth remained pin-point even after prolonged incubation. After 72 h incubation, the colonies were entire, grey, slightly glistening and non-hemolytic (Figure 1). A Gram stain showed long, pleomorphic Gram-negative bacilli (Figure 2). Curved cells, some curving back on themselves, were common, and many bacilli formed short chains of 3-4 cells. In addition, there were numerous bulbar swellings and blobs that also stained Gram-negative.

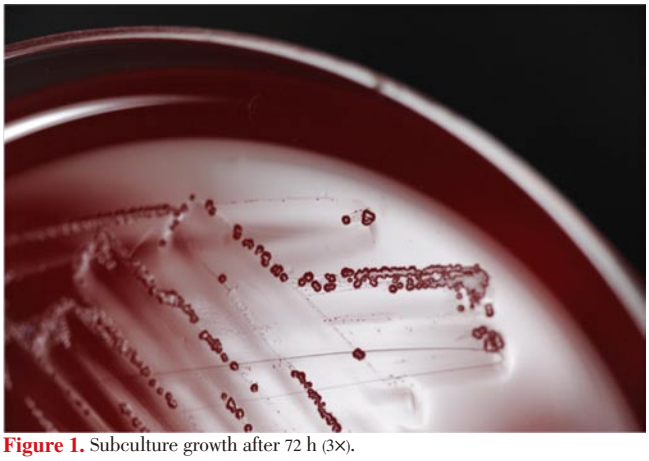

Figure 1. Subculture growth after 72 h (3×).

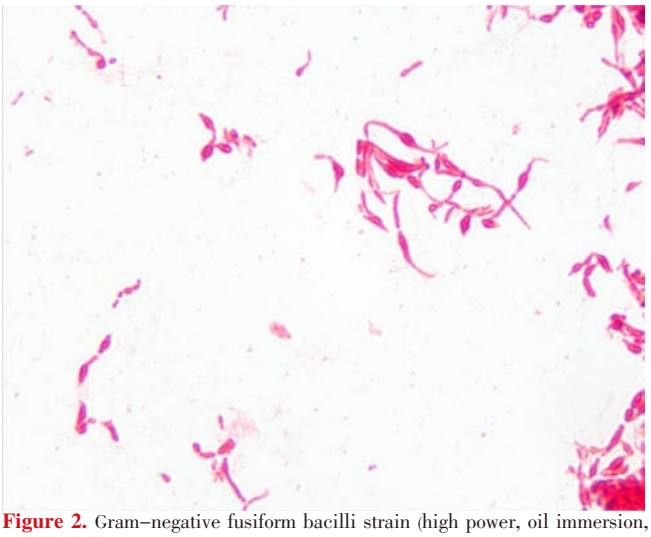

Figure 2. Gram-negative fusiform bacilli strain (high power, oil immersion, 1000×).

Routine biochemical testing was largely unrevealing in this inert organism, with negative reactions to oxidase, catalase, citrate and urease. Matrix-assisted laser desorption/ionization time of flight mass spectrometry analysis using the Bruker's IVD MALDI BioTyper (v2.2) gave a top identification of *S. moniliformis* with a score of 2.194. A 16S rDNA PCR-sequencing was performed to definitively identify the isolate. Susceptibility testing was attempted using Epsilometer test (AB Biodisk, Solna, Sweden) strips for penicillin and ceftriaxone. No growth was observed on this plate at all. As the organism grew fairly readily on standard blood agar medium, this was interpreted as the organism being exquisitely susceptible to the antimicrobials impregnated in the Epsilometer test strips, to such an extent that growth was completely inhibited in the medium. As the patient was showing convincing clinical response to his antimicrobial therapy, further attempts at *in vitro* testing were not pursued. Subsequent sets of blood cultures were negative.

On identification of *S. moniliformis*, the patient had already received 5 days of IV ceftriaxone and oral doxycycline. He was administered another 4 megaunits of IV benzylpenicillin. As he was clinically improving, with normalized total white cell counts (8.41×10^9/L) and down-trending C-reactive protein (29 mg/L), he was discharged 6 d after admission, with 3 more days of oral penicillin V. Transthoracic echocardiogram (9) excluded infective endocarditis prior to discharge.

3. Discussion

Two distinct organisms cause RBF, *S. moniliformis*, the etiologic agent in this case, and *Spirillum minus*, a

spirochetal organism that cannot be cultured on synthetic media. The latter is recognised to cause a form of RBF known as sodoku[1]. *S. moniliformis* is a saprophytic commensal of the rat oropharynx and is found in 10%-100% of domestic rats and 50%-100% of wild rats[1,7]. While the literature states that streptobacillary RBF is more common in North America and that sodoku is more common in Asia, recent case-reports have described streptobacillary RBF in India, Thailand, China and Singapore[8-11]. Indeed, this is the second case of streptobacillosis contracted in Singapore. The first case involved a 62-year-old man with suppurative polyarthritis in 2003[8]. The preponderance of recent literature highlighting streptobacillary RBF in Asia may be indicative of the relative difficulty in making a diagnosis of *Spirillum* RBF (for instance, *Spirillum minus* is unculturable using routine methods). However, it is perhaps time to rethink the dogmatic assertion prevalent in the literature about the distinct geographical distributions of these two organisms.

While the commonest known mode of infection is via a rat-bite, many patients would not recall being bitten. For instance, a case was reported of a patient who contracted RBF after disposing of a dead rat's carcass[12]. In addition, reports have demonstrated the presence of *S. moniliformis* in ferrets, gerbils, squirrels and domestic pets such as guinea pigs, dogs and cats[7]. To date, four proven cases of RBF after a dog bite have been reported[13]. While the typical victim of RBF in the past was an impoverished child, people at risk of RBF include pet-shop employees and laboratory technicians as rats are popular pets and study animals[1]. Of note, 55% of all *S. moniliformis* infections in the USA occur in children under the age of 12[14].

The disease caused by these 2 organisms have been well-described to manifest in 3 distinct clinical entities; streptobacillary RBF, sodoku (RBF caused by *Spirillum minus*) and ingested streptobacillary disease (Haverhill fever). The commonest, streptobacillary RBF, typically has an incubation of <7 d and presents with fever, rigors, migratory polyarthralgia and vague symptoms of an upper respiratory tract infection. The bite site typically heals rapidly with little local inflammation and no regional lymphadenopathy[1]. To date, the definitive review on RBF suggested from collated data that the symptoms from RBF are as such: fever (92%), polyarthralgia (66%), rash (61%), nausea and vomiting (40%), headache (34%), myalgia (29%) and sore throat (17%)[1]. This was seen in our patient, who presented with fever, myalgia, upper respiratory tract infection symptoms and a healed bite site. Sodoku is similar in presentation but has an incubation period of 14-18 d, with significant induration of the bite site and regional lymphadenopathy. In addition, joint involvement is rarer in sodoku[1].

On presentation, our patient complained of fever, vomiting and a sore throat. He did not have any other initial features of RBF. The wound on his foot was well-healed and barely visible. As he was well on return from Bangladesh and in the two-week interval prior to being bitten by a rat, we consider this to be an autochthonous case of RBF.

The third disease entity is Haverhill fever, caused by the ingestion of *S. moniliformis*. There have only been 3 reported outbreaks (Pennsylvania, USA 1925; Haverhill, Massachusetts, 1926; Essex, United Kingdom, 1983), all associated with the consumption of unpasteurized milk. In addition to the above symptoms, vomiting, headache and dizziness appear to be features of Haverhill fever[1].

The manifestations of complicated RBF are protean, the most feared is streptobacillary endocarditis. Approximately 20 cases of streptobacillary endocarditis have been reported in published literature, almost exclusively occurring in patients with underlying cardiac pathology such as underlying valvular abnormalities, prosthetic valves or congenital heart disease with a mortality rate of up to 25%[15]. In view of this, the authors of this paper advocate a transthoracic echocardiogram in every patient diagnosed with streptobacillary bacteremia, particularly if they are known to have underlying cardiac abnormalities of any kind. Streptobacillary arthritis is the second commonest complication of RBF has presented as monoarthritis, asymmetric oligoarthritis and even symmetrical polyarthritis in both suppurative and non-suppurative forms[8,11]. It may occur more commonly in the elderly, immunocompromised, diabetics and prosthetic joint implants[8]. As only 8.4% of patients with RBF-related septic arthritis have positive cultures, molecular methods of diagnosis should be considered in a persistent culture-negative monoarthropathy in the appropriate context[11,16,17]. Streptobacillary arthritis has not been associated with any mortality and has an excellent prognosis and recovery rate once antibiotics are instituted. Lastly, RBF can cause relapsing fever and an adequate history should be taken including animal exposure, ingestion of unusual foods and a travel history[18].

Given the relatively obscure and exceptionally fastidious nature of *S. moniliformis*, informing the microbiologist that RBF is suspected necessary as special culture media and molecular diagnostic tools are often required in clinching the diagnosis. It is worth noting that sodium polyanethol sulfonate (an anticoagulant additive to most blood culture sets) has been shown to inhibit the growth of *S. moniliformis* (this was fortuitously not observed in the first set of blood cultures drawn from the patient)[1]. Ideally, susceptibility

testing should be carried out to guide antimicrobial therapy. However, it should be noted that there are no established breakpoints for the susceptibility testing of this organism, either from the Clinical Laboratory Standards International or the European Committee on Antimicrobial Susceptibility Testing.

While treatment regimens may vary, IV benzylpenicillin is the antibiotic choice. Cephalosporins, tetracyclines and streptomycin have been used successfully in patients with penicillin allergy. However, erythromycin and minocycline have been implicated in treatment failure and probably should be avoided[1,19]. Streptobacillary endocarditis should be treated with dual therapy of IV benzylpenicillin and gentamycin[1]. Streptobacillary arthritis has demonstrated excellent response to single antimicrobial therapy that provided it has good penetration of the joints and synovium[20]. Antibiotics with poor penetration of the synovium such as aminoglycosides should probably be avoided in streptobacillary arthritis[20]. In view of the potential morbidity and mortality of RBF, all patients with rat exposure who are septic or have culture-proven bacteremia should be admitted for in-patient management. A case can be argued for a short course of prophylactic oral penicillin V in asymptomatic patients with rat bites, especially so for those who have risk factors for endocarditis or septic arthritis as previously discussed.

RBF is a rare infection that still bears reminding both in the developed and developing world. It should be suspected in patients who report a rat-bite or have contact with rats (*e.g.* pet-shop employees, pet owners, laboratory technicians). Under-recognition may lead to delays in treatment or inappropriate therapy and it has potentially catastrophic sequelae. Given its fastidious nature, communication between the microbiologist, infectious disease physician and primary physician is paramount to early diagnosis and management.

Conflict of interest statement

We declare that we have no conflict of interest.

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