CASE REPORT

An unusual tale of rat-bite fever endocarditis

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SUMMARY

A 49-year-old man presented to our department with an acute history of right leg tenderness, rash, swelling and fever. CT of the chest, abdomen and pelvis and a transoesophageal echocardiogram confirmed the diagnosis of mitral valve infective endocarditis with distal splenic emboli. Positive blood cultures revealed the causative organism to be *Streptobacillus moniliformis*. The patient was treated with high-dose antibiotics and had mitral valve replacement surgery.

BACKGROUND

Streptobacillus moniliformis is a fastidious, pleomorphic, non-capsulated, non-motile gram-negative bacillus found in the nasopharynx and oropharynx of rodents.¹ It is one of the two known causes of rat-bite fever, an underdiagnosed febrile illness characterised typically by fevers, myalgia, arthralgia and rash.² Infective endocarditis is a rare complication of *S. moniliformis* bacteraemia with only 22 cases having been published since 1915 and even fewer of those with embolic phenomena.³ We therefore believe this is an important case of a rare bacterial infection with atypical presentation and features.

CASE PRESENTATION

A 49-year-old homeless man with a history of previous alcohol dependency presented to the Accident and Emergency Department of Homerton hospital with a 6-day history of progressively worsening right leg pain, rash and swelling. The patient had recently been living in a shed squatting with three others. He often sourced food from shelters, shops and occasionally bins. He denied intravenous use of drugs and had no other relevant medical history of note. Clinical examination revealed a mild erythema over the anterior aspect of his right lower leg with mild calf swelling and tenderness on palpation. The patient also had epigastric tenderness. The rest of the examination was unremarkable. Full blood count revealed normocytic normochromic anaemia with haemoglobin of 10.5 g/dL and a mean cell volume of 94.1 fL. He had a normal white cell count and a raised C reactive protein of 117. His HIV serology was negative.

The initial impression was cellulitis with deep vein thrombosis; however, a venous doppler ultrasound was negative. He was started on empirical treatment for cellulitis with intravenous benzylpenicillin and flucloxacillin. Soon after admission, he became septic with high-grade fever (40°C). Serial sets of blood cultures were taken over 3 days as the patient continued to have high-grade fevers despite being on benzylpenicillin and flucloxacillin.

The aerobic bottle from the first set of blood cultures was positive after 24 h incubation in the Becton Dickinson BACTEC FX instrumented blood culture system in the microbiology laboratory at the Homerton hospital. The aerobic bottle from the second set of blood cultures flagged up as positive after 72 h incubation. Direct Gram stains from the positive blood culture bottles revealed long and thin filamentous gram-negative rods in loops and coils. The antibiotics were broadened to co-amoxiclav and gentamicin pending culture and organism identification.

A CT of the chest, abdomen and pelvis performed to exclude occult abscesses as a possible source for the patient's persistent fever and gram-negative septicaemia revealed splenic infarcts secondary to probable septic emboli (figure 1). He was re-examined for infective endocarditis as a possible source for the septic embolisation and was found to have an apical pan-systolic murmur and splinter haemorrhages. The remaining blood culture bottles were kept for extended incubation (10 days as opposed to the standard 5 days) as per laboratory protocol when investigating a case of infective endocarditis. The antibiotics were broadened empirically to meropenem and doxycycline.

INVESTIGATIONS

A portable transthoracic echocardiogram showed possible vegetation on the mitral valve, which was later confirmed with a transoesophageal echocardiogram (figure 2A, B).

The positive blood cultures were inoculated on blood, chocolate and MacConkey agar plates (oxid diagnostic media). These plates were incubated under aerobic, anaerobic and 5% CO₂-enriched environments in LEEC incubators. Small grey-white colonies were observed on the chocolate agar plate after 48–72 h of incubation in the CO₂-enriched environment. The organism was identified as a presumptive *S. moniliformis* using the Bruker biotyper microflex Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometer (MALDI-TOF MS) with ID scores of 1.8 and 2.1, respectively.

The isolate was sent to Micropathology Ltd, Coventry for 16S ribosomal RNA (rRNA) gene detection and sequencing, which confirmed the identification as *S. moniliformis*. Micropathology Ltd uses a specific extraction process and an in-house amplification assay to extract and amplify the 16S rRNA gene.⁴ The amplified product is sequenced in-house at Micropathology Ltd (based on Sanger sequencing) using Applied Biosystems Instruments (ABI) 3130xl genetic analyser in combination with ABI BigDye 3.1 technology.⁵ The sequences are then compared to known sequences available in Genbank⁶ using the BLAST tool.⁷

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Figure 1 CT scan showing two individual splenic infarcts.

When questioned further, the patient denied any recent animal bites and contact with any rodents. However, given the nature of his social circumstances, it is possible that he may have been in contact indirectly with *S. moniliformis* through contaminated food products as has been reported in some previous cases.⁸

Bartellonella, Brucella and Coxiella serology, which was sent as part of the workup of gram-negative infective endocarditis, was negative. Unfortunately, the organism failed to grow for susceptibility testing.

A transoesophageal echocardiogram confirmed the presence of large vegetation on a posterior leaflet of the mitral valve (figure 2B). A perforation of P3 was also noted, resulting in mild mitral regurgitation. Both the transthoracic and transoesophageal echocardiogram showed no evidence of previous valvular or structural abnormality.

TREATMENT

Following the identification of the bacteria, the patient was started on intravenous high-dose benzylpenicillin 2.4 g four hourly (to cover for potential L form variants) and oral doxycycline 100 mg twice daily was continued.

The patient responded well to treatment and the initial presenting cellulitis resolved. The patient was scheduled to have

mitral valve replacement surgery after discussion with the cardiothoracic team at St Bartholomew's hospital due to the possibility of septic embolisation.

OUTCOME AND FOLLOW-UP

He was transferred to St Bartholomew's hospital after 6 weeks of antibiotic therapy where he had a tissue mitral valve replacement. The microscopy, culture and sensitivity, 16S rRNA gene sequencing and histopathology of the mitral valve tissue were negative for *S. moniliformis*. A postoperative echocardiogram showed no vegetation, a functioning prosthetic mitral valve and the antibiotics were stopped. He remained an inpatient while suitable accommodation postdischarge was arranged and will be followed up in the outpatients' clinic in 3 months' time.

DISCUSSION

Rat-bite fever is a zoonotic disease that encompasses two different disease syndromes dependent on the causative organism: *S. moniliformis*, as outlined in this case, and *Spirillum minus*. Geographically, *S. moniliformis* is more commonly found in North America and Europe, whereas *S. minus* (also known as Sodoku) has been reported more frequently in Asia.^{2 9} Clinically, they share similar symptoms: fever, arthralgia, arthritis, headache, malaise and rash. The differentiating features of *S. minus* include

Figure 2 (A) Transthoracic echocardiogram showing a large vegetation on a posterior leaflet of the mitral valve. (B) Transoesophageal echocardiogram showing a large vegetation on a posterior thickened leaflet of the mitral valve. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 1 A modified up to date version of McCormack *et al's*¹⁴ table showing all the reported cases of *Streptobacillus moniliformis*-associated endocarditis since 1915^{3 8}

Year ^{ref}	Age	Sex	Underlying heart disease	Rat exposure	Clinical presentation	Echocardiogram	Blood cultures	Treatment	Outcome	Embolic phenomena
1915 ^{3 8}	67	F	None	Rat bite	Fever, rash, murmur			None	Died	Confirmed at autopsy
1934 ³	18	M	RHD	NS	Incomplete description			None	Died	None
1940 ^{3 8}	14	F	None	Rat bite	Fever, anaemia, murmur			None	Died	Confirmed at autopsy
1944 ^{3 8}	43	M	RHD	Rat exposure	Fever, rash, murmur			Penicillin 200 000 U	Died	Confirmed at autopsy
1945 ⁷	22	M	RHD	NS	Murmur, petechiae			Penicillin 300 000 U	Died	Possible CNS insult
1947 ³	17	F	NS	NS	Incomplete description			Penicillin 400 000 U	Died	None
1949 ³	40	M	RHD	Rat exposure	Murmur, splenomegaly, Osler nodes, anaemia			Penicillin 1 million units	Cured	Possible
1949 ³	27	M	RHD	Handled dead rat	Fever, murmur			Penicillin 1.2 million units+chloramphenicol	Cured	None
1952 ³	54	M	None	Rat bite	Fever, rash, murmur,			Penicillin 3 million units	Cured	None
1967 ³	70	F	Calcified AS		Fever, splenomegaly, murmur, anaemia			Penicillin 1.8 million units	Cured	Possible
1967 ³	43	M	NS	Rat bite	Fever, arthritis, murmur, pericardial effusion			Penicillin 10 million units	Died	None
1967 ³	60	M	RHD	Rat exposure	Fever, murmur			Penicillin 12 million units	Cured	None
1981 ³	41	M	None	Rat bite	Fever, murmur, heart failure			Penicillin 40 million units+gentamicin	Died	None
1985 ³	3 months	M	None	Rat bite	Fever lethargy			None	Died	None
1985	63	F	None	Rat bite	Fever, arthritis, murmur			Penicillin 20 million units+amikacin	Cured	None
1986 ³	8	M	RHD	None	Fever, murmur, hepatosplenomegaly			Penicillin 50 000 U/day	Cured	Possible
1989 ³	2 months	?		Rat bite	Fever, pneumonia, hepatosplenomegaly, meningitis	Autopsy: fibrinous endocarditis			Died	Possible
1992 ³	46	M	None	Rat bite	Fever, arthritis, murmur, hepatomegaly, ventricular bigeminy	Thickened AV. No veg	Positive	Penicillin 24 million+tetracycline 500 mg Q6H	Cured	Possible
2000 ⁶	37	M	NS	Rat bite	Fever, polyarthralgia,	Veg+MR valve rupture	Positive	Ceftriaxone 2 g/day 3 weeks+gentamicin 120 mg/day 2 weeks+penicillin 24 million 1 week		None
2006 ³	18	M	Small VSD	Rat bite		TV veg small VSD	Positive	Penicillin 12 million units+gentamicin 50 mg Q8H 4 weeks	Cured	None
2007 ³	29	M	NS	Rat bite	Fever, dizziness, lethargy	Large veg/AR/severe LV dysfunction (TEE)	Explanted AV +ve culture	Ampicillin+ceftriaxone+gentamicin+AVR+Ampicillin +ceftriaxone+gentamicin+AVR+penicillin/fosfomycin/ gentamicin posoperative	Cured	None
2007 ³	60	F	S/P MVR	Rat bite	Fever, intermittent leg wound	Prosthetic MV dehiscence+MR+veg	Positive	Redo MVR+levoflox 500 mg OD+ceftriaxone 1 g Q12H+intravenous gentamicin 1 mg/kg Q8H	Cured	None
2013 ³	44	M	None	Rat bite	Fever	MV veg+severe MR	Positive	Penicillin 12 million units+gentamicin	Cured	None
2014 (present case)	49	M	None	Possible rat exposure	Myalgia, fever	Large veg, MV+MR	Positive	Penicillin 2.4 g 4H+doxycycline 100 mg BD+MVR 6 weeks	Cured	Confirmed with CT

AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVR, AV replacement; BD, twice daily; CNS, central nervous system; F, female; LV, left ventricular; M, male; MR, mitral regurgitation; MV, mitral valve; MVR, MV replacement; NS, not significant; OD, once daily; RHD, rheumatic heart disease; TEE, transthoracic echocardiogram; TV, tricuspid valve; veg, vegetation; VSD, ventricular septal defects.

recurring fever, a large macular rash, lymphadenopathy and a longer incubation period.^{3 9}

As the name suggests, the carriage of both these organisms is in the upper respiratory tracts of rats and is transmitted through either a scratch or a bite from an infected animal or consumption of contaminated food or water. Alternative animal vectors have been described in the literature including mice, gerbils, ferrets and even turkeys.^{2 9}

S. moniliformis is a fastidious, pleomorphic, non-capsulated, non-motile gram-negative bacillus.¹ It is the solitary member of the genus *Streptobacillus* and, based on 16S rRNA sequencing, is currently classified in the family Fusobacteriaceae, class Fusobacteria and phylum fusobacteria.¹⁰

Blood (10 mL) must be ideally anticoagulated with citrate (10 mL sodium citrate, 2.5%) prior to processing as it is inhibited by the anticoagulant sodium polyanethol sulfonate (SPS).^{11 12} However, *S. moniliformis* has been successfully recovered from SPS-containing blood culture media with resins (BACTEC Peds-Plus, BD Biosciences).¹³

S. moniliformis has historically been associated with several serious complications, including endocarditis, pericardial effusion and meningitis, as described by Elliot 2007. Endocarditis is the most commonly reported complication with 22 cases of *S. moniliformis* associated endocarditis previously described; please table 1 below.

Endocarditis is not only the best described complication, but also that with the highest mortality.² Of the 22 cases with reported outcomes between 1915 and 2013, 10 have died. However, as suggested by Rordorf *et al*, of these 10 cases, the majority received non-specific antibiotic regimens or inadequate penicillin dosing.^{15 16} The current recommended treatment for rat-bite fever is 1.2 million units of intravenous penicillin G per day.^{1 2} However, in the case of infective endocarditis, this dose should be increased to 4.8 million units intravenously per day.²

Rupp,⁸ first highlighted that the majority of the cases had a predisposing valvular abnormality: commonly rheumatic heart disease. At present, this remains true, with 10 of the 18 cases with reported underlying valvular pathology.

The case documented above is exceptional insofar as it has confirmed radiological evidence of embolic phenomena. Clinical features including fever, murmur and rash are all well documented; however, distal emboli has been an infrequent finding.⁸ Petersen *et al*,¹⁷ reported that a patient might have had a possible major embolic central nervous system event following treatment and another patient with transient splenomegaly, suggestive of embolic phenomena. He goes on to describe a further three cases with confirmed splenic and renal infarcts at autopsy that one might assume were directly associated with infective endocarditis. In more recent literature, there have been four reports of patients with either isolated splenomegaly or hepatosplenomegaly² potentially indicative of distal emboli. However, there is no recorded radiological evidence to support this, possibly as a result of inadequate imaging modalities. This lack of availability is also demonstrated by the fact that only six cases have had an echocardiogram.

S. moniliformis endocarditis is a rare complication of rat-bite fever and emphasises the importance of a thorough history in a patient with atypical social circumstances. Early suspicion and diagnosis, with prompt treatment with penicillin, is paramount.

Learning points

- ▶ Rat-bite fever is a rare underdiagnosed febrile illness that should be considered in patients with fever of unknown origin and atypical social circumstances.
- ▶ The fastidious nature of *Streptobacillus moniliformis* makes it very difficult to isolate from blood cultures. This means that diagnosis relies heavily on clinical suspicion, with close and early liaison with microbiology being paramount in the treatment of this condition.
- ▶ The use of citrated blood, selective media, automated identification systems and molecular techniques can help in the early identification of this organism.
- ▶ The efforts of a multidisciplinary team comprising cardiologists, microbiologists, radiologists, cardiothoracic surgeons in secondary care and involvement of general practitioners in a primary care setting were instrumental in the management of our challenging case

Competing interests None.

Patient consent Obtained.

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