Streptococcus intermedius masquerading as fungal infective endocarditis

Introduction

Infective endocarditis remains an important clinical entity with an incidence of 1.7–10/100 000 person years (Marks et al, 2015). Despite improvements in health care, it still results in significant morbidity and in-hospital mortality approaches 16% (Marks et al, 2015). There are likely multiple causes including late diagnosis, poor response to therapy and the challenges in identifying the causative pathogen and instigating the correct treatment. This is particularly the case for causative organisms that are difficult to culture or identify using routine laboratory methods.

An example of this is *Streptococcus intermedius*, which belongs to the *S. milleri* group along with other two species (*S. anginosus* group and *S. constellatus*). It is a commensal organism that can turn into an opportunistic pathogen (Whiley et al, 1992). It is a rare cause of infective endocarditis and may initially present with abscesses in the liver, spleen or brain which may mimic fungal infection (Woo et al, 2004; Rashid et al, 2007; Tran et al, 2008). Difficulty in identifying this organism has led to the development of molecular testing to aid diagnosis. To the authors' knowledge, there are very few cases in the literature of infective endocarditis caused by *S. intermedius* that have been confirmed using 16S polymerase chain reaction (Woo et al, 2004). This article describes a patient presenting with *S. intermedius* infective endocarditis which was diagnosed using this method.

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Discussion

S. intermedius is an anaerobic, Gram-positive organism that belongs to the *S. milleri* group. It can be part of the normal flora of the oral cavity, upper respiratory tract or gastrointestinal tract, but can also be an opportunistic pathogen (Whiley et al, 1992). *S. intermedius* is usually found as a solitary isolate associated with deep-seated purulent abscesses – typically found in the brain and liver – and is rarely a causative agent in cases of infective endocarditis (Woo et al, 2004). Phenotypic differentiation of members of the *S. milleri* group can be difficult, and has

CASE REPORT

A 77-year-old man presented to the emergency department with rigors, fevers and confusion. His background included hypersensitivity pneumonitis for which he had been taking azathioprine 100 mg once per day for approximately 4 years before the current admission. On examination, he was pyrexial at 38°C and photophobic. He had a soft pan-systolic murmur in the apical region, radiating to the left axillary area, but no peripheral stigmata of endocarditis. Initial investigations demonstrated a white cell count of $20x10^9$/litre (neutrophil $18x10^9$/litre, lymphocytes $1.14x10^9$/litre, monocytes $0.75x10^9$/litre and eosinophil $0.03x10^9$/litre), C-reactive protein 57 mg/litre and creatinine 83 μmol/litre. In view of his history, magnetic resonance imaging of his brain was performed which demonstrated appearances in keeping with multiple cerebral abscesses (*Figure 1*). CSF analysis showed high protein (0.73 g/litre) and low glucose levels (1.9 mmol/litre). His initial blood and CSF cultures were negative.

The most likely cause was thought to be a fungal infection, given the magnetic resonance imaging appearance of multiple (rather than a solitary) abscesses with basal ganglia involvement on a background of immunosuppression. He was treated empirically with liposomal amphotericin B in addition to broad-spectrum antibiotics including ceftriaxone and co-trimoxazole while awaiting culture confirmation.

As part of his work up, and as there was concern that his presentation could be accounted for by a cardio-embolic phenomenon, a transthoracic echocardiogram was performed. This demonstrated a mobile lesion attached to the posterior leaflet of the mitral valve (*Figure 2*) with concomitant severe mitral regurgitation. Unfortunately, transoesophageal echocardiography was limited because of the presence of a large hiatus hernia and inability to adequately visualize the cardiac valves.

Following 2 weeks of therapy, blood cultures remained negative. However, his C-reactive protein level decreased from 57 mg/litre to 4 mg/litre and his Glasgow Coma Scale improved from 12 to 15. An interval magnetic resonance imaging scan of his brain demonstrated improvement in the number and volume of abscesses (*Figure 3*). In view of the improvement in his clinical state, despite no definitive pathogen having been identified, he was transferred to the local cardiothoracic tertiary centre for an urgent mitral valve replacement.

Molecular testing was performed on the excised valve. The 16S gene was amplified by polymerase chain reaction using primers described in Harris and Hartley (2003) and HotStar Taq Plus PCR mastermix (Qiagen, Hilden, Germany), according to the manufacturer's instructions, with an annealing temperature of 60°C. The polymerase chain reaction amplicon underwent Sanger sequencing using BigDye Terminator v1.1 Cycle Sequencing kit (Thermo Fisher Scientific, Hemel Hempstead, UK). 16S derived sequences were compared to the GenBank database, which identified *Streptococcus intermedius*, with a percentage identical base pair value >95% considered acceptable for species level identification.

The patient made an uncomplicated recovery and completed 6 weeks of antibiotic therapy.

Figure 1. Axial T1-weighted post contrast magnetic resonance imaging showing ring enhancement abscesses (arrows).

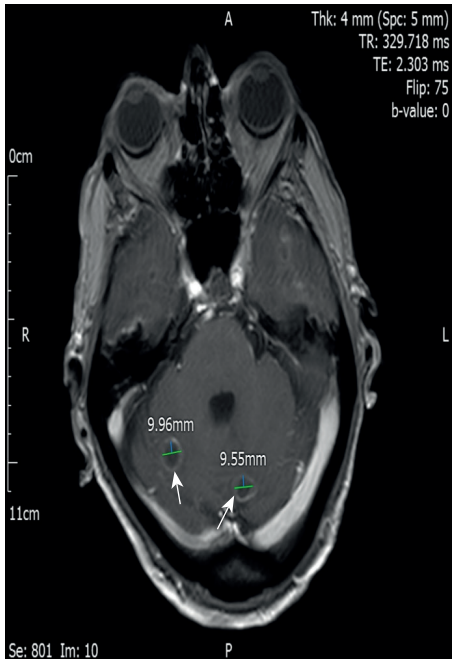
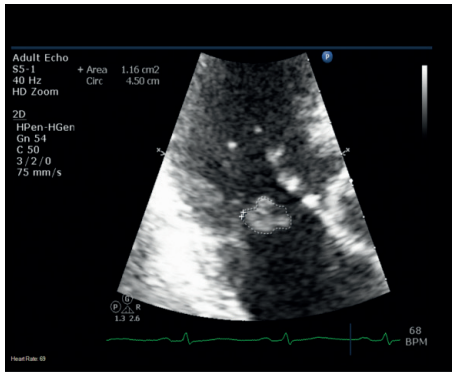


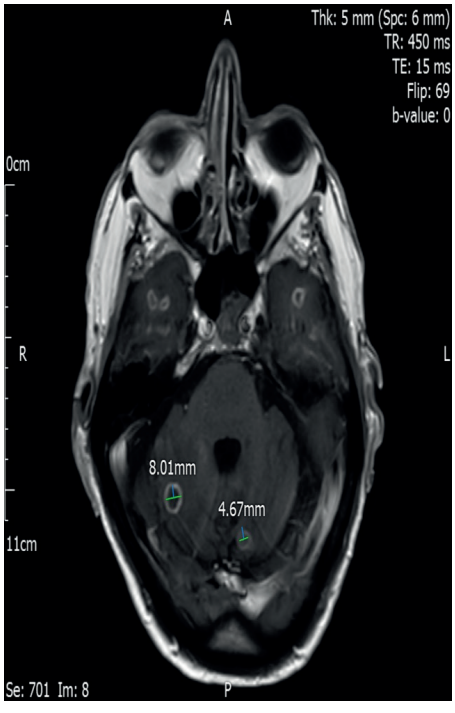
Figure 2. Three chamber echocardiogram showing 1.16 cm^2 mass on the posterior leaflet of the mitral valve.



resulted in the development of genotypic methods using polymerase chain reaction to aid in the speciation of these organisms (Clarridge et al, 2001).

In most previous reports on cases of infective endocarditis caused by the *S. milleri* group, the exact species was not mentioned. A retrospective study by Woo et al (2004) was the first to show a direct relationship between *S. anginosus* and infective endocarditis by applying 16S rRNA sequencing to six cases of *S. milleri* group endocarditis, all of which were identified as being caused by *S. anginosus*.

Figure 3. Two-week interval axial T1-weighted post contrast magnetic resonance imaging showing improvement in the number and volume of abscesses.



S. intermedius very rarely causes infective endocarditis – the first case confirmed by 16S sequence analysis was reported by Tran et al (2008).

To the authors' knowledge, this report describes the second case of *S. intermedius* endocarditis to be confirmed by this assay.

Conclusions

Infective endocarditis caused by *S. intermedius* is uncommon. The most common presentation is with brain abscesses that mimic fungal infection. The difficulties in distinguishing organisms of the *S. milleri* group make it hard to determine their pathogenic potential. This case demonstrates the importance of thorough clinical work up of patients and the use of polymerase chain reaction as a useful adjunctive tool in the management of patients with endocarditis, especially in those with culture-negative infections and atypical organisms, thereby reducing the risk of unnecessary and prolonged exposure to antibiotics.

Additional reports are required to more accurately determine the predominance and variety of clinical disease resulting from infection with *S. milleri* group organisms. BJHM

LEARNING POINTS

- The *Streptococcus intermedius* group of organisms is a rare cause of endocarditis, which may initially present with abscesses in the liver, brain or spleen.
- These infections can mimic fungal infections.
- The 16S polymerase chain reaction technique can be a useful adjunctive tool to identify organisms in culture-negative infections, to reduce the risk of unnecessary and prolonged exposure to antibiotics.

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