CASE REPORT

Prosthetic valve endocarditis caused by *Propionibacterium* species successfully treated with coadministered rifampin: report of two cases

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SUMMARY

We describe two cases of prosthetic valve endocarditis caused by *Propionibacterium* spp. successfully treated with a combination of rifampin and intravenous penicillin. Rifampin was chosen due to its promising activity against planktonic and biofilm *Propionibacterium*, its favourable minimal inhibitory concentrations, its excellent oral bioavailability and tissue penetration.

BACKGROUND

Propionibacterium sp. is increasingly reported to be the causative pathogen in severe systemic infections, especially in foreign-body-associated infections. In case of infective endocarditis (IE), *Propionibacterium* sp. is usually involved in prosthetic valve IE. There are no guidelines which specifically address the management of *Propionibacterium* endocarditis.

CASE PRESENTATION

Case 1

In September 2011, a 70-year-old woman, who underwent biological aortic valve replacement surgery 3 months before, was admitted to our hospital with fever and cough for more than 1 week. Two sets of blood cultures were taken 8 days before admission and an empirical antibiotic treatment with oral amoxicillin in combination with clavulanic acid was started at that time by her external cardiologist. In these blood cultures *Propionibacterium avidum* was growing. Physical examination showed a temperature of 37.6° with otherwise unremarkable vital parameters, a 3/6 holosystolic cardiac murmur and splinter haemorrhages of her right thumb. Laboratory tests revealed an elevated C reactive protein (CRP) of 208 mg/l (standard value <5). Transoesophageal echocardiography (TEE) showed multiple vegetations on the biological aortic valve up to 15 mm and a perivalvular abscess. Antibiotic treatment was switched to high-dose intravenous penicillin and gentamicin. Due to perivalvular abscess leading to a complete heart block with haemodynamic intolerance, the bioprosthetic valve replacement had to be performed already 2 days after admission. The Gram stain of the aortic vegetation was negative, but after 14 days *P. avidum* had grown in the culture. The minimal inhibitory concentration (MIC) was 0.047 mg/l for penicillin and 0.004 mg/l for rifampin. Gentamicin was stopped and rifampin was added to penicillin. The patient was discharged 2 weeks after admission for rehabilitation and treatment was continued for another

4 weeks. After 6 weeks of treatment, the patient was clinically unremarkable but the CRP was still elevated with 40 mg/l. Transthoracic echocardiography (TTE) showed no vegetation and there was no clue for a nosocomial infection. Eosinophil granulocytes were slightly elevated. The differential diagnosis included an incompletely controlled endocarditis, a drug-related allergic reaction or an infected aneurysm of the right subclavian artery, which was initially described in a CT scan. We changed to a non-penicillin-based oral regimen consisting of ciprofloxacin (MIC 0.38 mg/l) combined with rifampin for another 6 weeks, resulting in a normal CRP. After a total of 12 weeks we stopped the antibiotic therapy. Seven months later neither clinical nor laboratory results raised any concern for relapse of IE.

Case 2

In August 2011, a 58-year-old man was admitted to our stroke unit with sudden onset aphasia. His medical history was remarkable for a biological aortic valve replacement and an aortocoronary bypass surgery 2 years before. In May 2011, a hernia repair was performed. One week before admission he was treated with ciprofloxacin for 7 days due to malaise and shivering. At the time of admission the patient was febrile (temperature 38.2° C) with otherwise normal vital parameters. Cardiac examination demonstrated a previously documented 4/6 systolic murmur and no other signs of endocarditis were observed. Two sets of blood cultures were drawn. The CT scan of the head revealed ischaemia in the basin of the right media artery and acute thrombolysis was performed. TTE was unremarkable, showing a good function of the aortic prosthesis and no vegetations. Although the patient did not suffer from typical symptoms related to cystitis, the initial assessment of the neurologists led to the suspicion of urosepsis and an empiric treatment with amoxicillin in combination with clavulanic acid was started. Fever persisted and TEE was performed revealing vegetations at the biological aortic valve. Treatment was switched to vancomycin, gentamicin and rifampin. Ten days after admission two blood cultures revealed growth of *Propionibacterium acnes*. We decided to continue the antibiotic treatment with vancomycin, rifampin and gentamicin because we could not rule out a contamination of the blood specimen with *P. acnes*. Furthermore MIC for *P. acnes* was favourable. Due to recurrent febrile episodes with evidence of splenic abscess, the spleen

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was removed 14 days after admission. Valve surgery had to be delayed due to haemorrhagic imbibition of the ischaemic cerebral area. Even after splenectomy the febrile episodes persisted. A drug fever to rifampin was suspected and antibiotic treatment was changed to vancomycin (MIC 0.5 mg/l) and levofloxacin (MIC 0.5 mg/l). TEE 3 weeks after admission demonstrated a new paravalvular aortic abscess and the patient underwent replacement of the aortic root and the bioprosthesis with a mechanical conduit. The Gram stain of the aortic valve showed Gram-positive rods, confirmed as *P. acnes* by PCR. We switched the antibiotic treatment to intravenous penicillin G 4 million international units every 4 h (MIC 0.094 mg/l) in combination with rifampin 450 mg orally twice daily (MIC 0.006 mg/l). The antibiotic treatment was postoperatively continued for 6 weeks. Due to catheter-related infection with coagulase negative *Staphylococcus*, vancomycin was added for 2 weeks. Eight months after the end of treatment, the patient showed no signs of relapse of an IE.

DISCUSSION

These two cases demonstrate unique features of prosthetic valve IE caused by *Propionibacterium* sp. Infections associated with this bacterium have been increasingly reported.¹ This may be explained by two factors: first, microbiological techniques to diagnose *Propionibacterium* sp. have improved. Second, foreign-bodies are more frequently used and *Propionibacterium* sp. is associated with foreign-body infections as this microorganism has the ability to produce biofilms.² Previous surgery at the site of *Propionibacterium* infection is noted in up to 85%.³ Since *P. acnes* is part of the skin flora one could argue that in case two the hernia repair 3 months before admission led to the inoculation of *P. acnes*. This bacterium can remain intracellular in a dormant state for weeks and months, which explains the long incubation period.³ In a prospective cohort study the diagnosis of IE occurred after a mean interval of 14 years following valve replacement.⁴ The median age of affected patients with IE is about 50 years, with up to 90% being men.⁵ This may reflect the higher rate of implantation of prosthetic devices in men. Although *Propionibacterium* bacteraemia is traditionally considered to be a contaminant and of non-invasive nature, in the last decade *Propionibacterium* sp. turned out to be the causative pathogen in severe infections.⁶ Evidence of *Propionibacterium* bacteraemia from patients with foreign-bodies or predisposing conditions like congenital heart disease should always raise clinical suspicion of infection. Both cases highlight the problem of interpreting positive blood cultures, since initially a contamination could not have been excluded. To exclude contamination from real infection, several sets of blood cultures should be drawn. However, the positivity rate of blood cultures taken in *Propionibacterium* IE is reported to be only 50%.⁶ In case of *Propionibacterium* IE, fever can be documented in approximately 75%, but symptoms such as night sweat, weight loss, chills, arthralgias and subfebrile temperatures are often unspecific.⁵ In an analysis of 524 episodes with *Propionibacterium* bacteraemia, only 20 patients (3.8%) showed a systemic inflammatory response syndrome. These characteristics are explained by low virulence of this pathogen. The reported mean time for isolation is 6 days (range 3–19) for blood cultures and 4.7 days (range 2–14) for other specimens.³ With the new blood culture systems incubation for 7 days is sufficient; longer incubation is mandatory for the older blood culture systems. Currently, there is no consensus on how to treat a *Propionibacterium* IE. Most authors suggest a course of 6 weeks with a betalactam antibiotic (mostly penicillin) in combination with an aminoglycoside for

2 weeks. Other antibiotic regimens refer to vancomycin, ceftriaxone, clindamycin and daptomycin.^{6–7} Treatment with rifampin in *Propionibacterium* endocarditis has been reported earlier in three articles.^{6–8–9} In our first case we prolonged the antibiotic treatment with rifampin and ciprofloxacin, since we could not rule out an incompletely controlled endocarditis. The second case was complicated by a splenic abscess and a para-aortic abscess formation despite treatment with vancomycin, aminoglycoside and rifampin. In our opinion the reasons could be twofold: (1) valve surgery was too late although an earlier intervention was not possible¹⁰ and (2) antimicrobial susceptibility of *P. acnes* to vancomycin was presumably reduced in the biofilm on the affected valve. Trampuz *et al* recently published data about the efficacy of rifampin alone and in combination with either vancomycin, daptomycin or levofloxacin against biofilm *P. acnes* in vitro and in a foreign-body infection model. Rifampin in combination with daptomycin showed cure rates of 63%, whereas cure rates of rifampin in combination with vancomycin and levofloxacin were 46% and 25%, respectively. Based on in vitro biofilm studies, the combination of rifampin and penicillin G may represent an alternative to rifampin and daptomycin, but authors were not able to investigate this in their animal model.¹¹

In conclusion, *Propionibacterium* IE should be suspected in patients with prosthetic heart valves even if they present with unspecific symptoms, and apart from antimicrobial treatment, the threshold for surgical intervention should be low. We strongly believe that a rifampin-containing treatment in combination with daptomycin or penicillin G should be considered in the case of a *Propionibacterium* prosthetic IE due to its promising activity against planktonic and biofilm *Propionibacterium*, the very low MIC, the excellent oral bioavailability and the high tissue penetration. For maintenance therapy in complicated IE the combination of rifampin with ciprofloxacin might be a reasonable alternative with excellent oral bioavailability.¹²

Learning points

- ▶ *Propionibacterium* infective endocarditis (IE) should be suspected in patients with prosthetic heart valves even if they present with unspecific symptoms.
- ▶ Apart from antimicrobial treatment the threshold for surgical intervention should be low.
- ▶ A rifampin-containing treatment in combination with daptomycin or penicillin G should be strongly considered in the case of a *Propionibacterium* prosthetic IE.
- ▶ The combination of rifampin with ciprofloxacin might be a reasonable alternative with excellent oral bioavailability for maintenance therapy in complicated IE.

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Competing interests None.

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