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Case report

Effectiveness of daptomycin against infective endocarditis caused by highly penicillin-resistant viridans group streptococci

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ABSTRACT

Penicillin-resistant viridans group streptococci (VGS) infections are an emerging issue in infectious diseases. Here, we present a case of mitral valve infective endocarditis caused by highly penicillin-resistant VGS (minimum inhibitory concentration >4 μg/mL), which was successfully treated with daptomycin. Although the clinical efficacy of daptomycin has not been established, it can be an alternative for the treatment of highly resistant VGS endocarditis.

Introduction

Reported as a frequent pathogen, viridans group streptococci (VGS) are responsible for 40–60 % of community-acquired native-valve endocarditis cases [1]. The number of VGS cases that were relatively or fully resistant to penicillin has been increasing over the decades and is an emerging issue in the field of infectious diseases [2]. As previously reported [3], the frequent long-term use of amoxicillin may induce VGS resistance to penicillin. We present a case of mitral valve infective endocarditis caused by highly penicillin-resistant VGS (minimum inhibitory concentration [MIC] >4 μg/mL), which was successfully treated with daptomycin.

Case report

A 35-year-old healthy woman had a past medical history of recurrent chronic sinusitis over several years and had been previously treated with amoxicillin-clavulanate and levofloxacin. She presented to our outpatient clinic with a two-week history of fever with temperatures up to 38 °C. Nine days before her first clinic visit, she was prescribed amoxicillin-clavulanate. On admission, the patient's state was stable with clear consciousness, a temperature 37.6 °C, blood pressure 120/50 mmHg, heart rate 90 beats/min, and respiratory rate 16 breaths/min, and her oxygen saturation, measured by pulse oximetry, was 98 % on room air. The patient was noted to have a pan systolic murmur on the right sternal border and apex (Levine 4/6). She also had tenderness on the left, upper quadrant and had conjunctival petechiae and Janeway lesions on her left thigh. Laboratory findings revealed elevated white blood cell count 10,800/μL, hemoglobin level 12.6 g/dL, platelet count 410,000/μL, creatinine level 0.59 mg/dL, and C-reactive protein level 10.2 mg/dL. Transthoracic and transesophageal echocardiography revealed a mobile vegetation measuring 17 mm × 5 mm on her mitral valve associated with moderate mitral regurgitation (Fig. 1). A contrast whole trunk computed tomography scan revealed low-density attenuation in the spleen (Fig. 2) and an aneurysm measuring 6 mm in diameter in the superior mesenteric artery (SMA). Brain MRI indicated a cerebral infarction measuring 1 cm in diameter on the right occipital lobe. The patient was diagnosed with infective endocarditis in the mitral valve associated with multiple septic emboli, including splenic emboli, in addition to an SMA and cerebral artery aneurysm. As the vegetation was large, she underwent urgent mitral valve replacement with a biological valve on the same day.

Ampicillin/cloxacillin intravenously (IV) 4 g every 4 h, ceftriaxone IV 2 g every 12 h, and vancomycin IV 1 g every 12 h were begun. On day 2, three sets of blood cultures (aerobic and anaerobic bottles for

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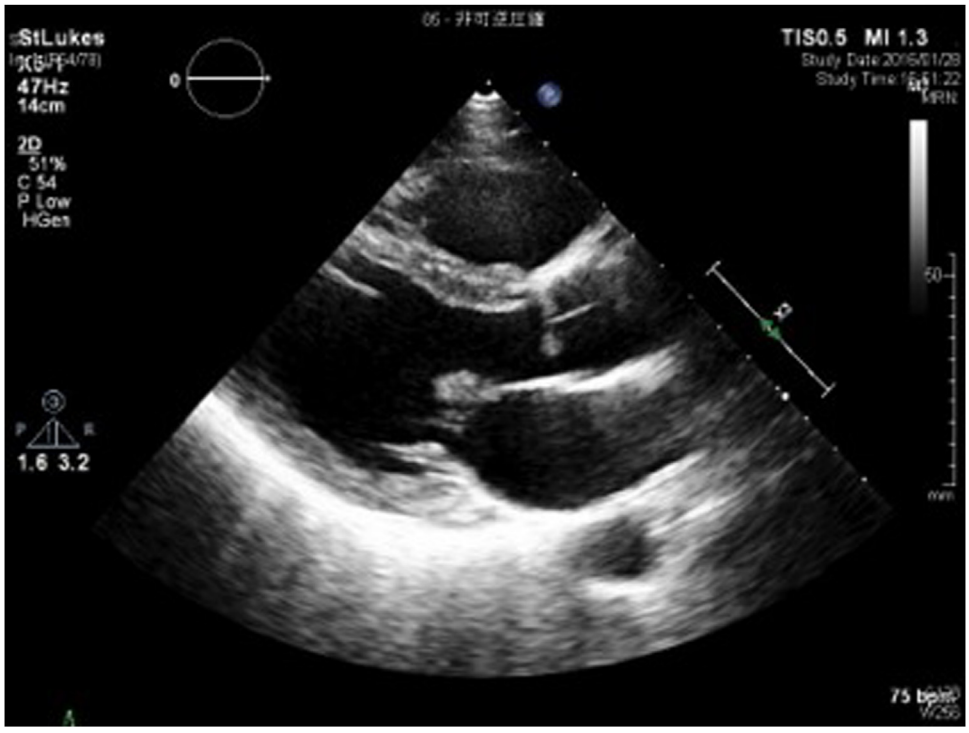

Fig. 1. Transthoracic echocardiogram revealed a mobile vegetation measuring 17 mm × 5 mm on the mitral valve.

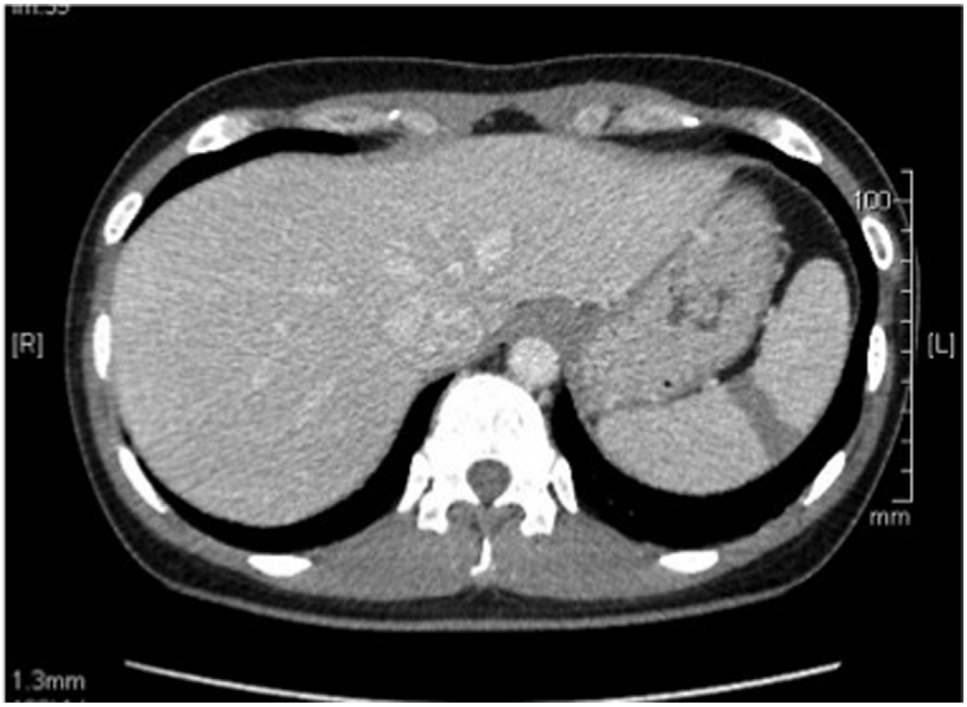

Fig. 2. A contrast whole trunk computed tomography scan revealed low-density attenuation in the spleen.

each set), obtained during admission, grew gram-positive cocci in chains, which was finally identified as *Streptococcus mitis/oralis* by VITEC 2 GP ID card (bioMérieux) and matrix-assisted laser desorption/ionization–time of flight mass spectrometry equipment, MALDI Biotyper (Bruker). Antimicrobial susceptibility testing was performed using the Mueller Hinton broth with 3% lysed horse blood using an MF 7 J panel in MicroScan Walkaway 96 plus (Beckman Coulter). MICs were as follows: penicillin G 4 μg/mL, cefotaxime 4 μg/mL, and vancomycin 1 μg/mL. MICs measured using Etest (bioMérieux) are also shown in Table 1 (daptomycin 0.25 μg/mL and meropenem 1.0 μg/mL). More than likely, because of hypoperfusion during surgery and the effect of multiple antimicrobial agents, acute kidney injury (creatinine level increased to 4.2 mg/dL) occurred on hospital day 3.

Based on this susceptibility result and acute kidney injury, antimicrobial therapy was switched to daptomycin IV 10 mg/kg

Table 1
Susceptibility testing of *Streptococcus mitis/oralis*.

	MicroScan WalkAway 96 plus, MIC (μg/mL)	E test, MIC (μg/mL)	Susceptibility according to CLSI M100-28 breakpoints
Penicillin G	4	4	Resistant
Cefotaxime	4	6	Resistant
Meropenem	2	1	Susceptible
Vancomycin	1		Susceptible
Daptomycin	NA	0.25	Susceptible
Cefotiam	>4		No data
Erythromycin	1		Resistant
Levofloxacin	1		Susceptible

MIC: Minimal inhibitory concentrations, NA: not available.
CLSI: Clinical Laboratory Standards Institute.

every 48 h plus levofloxacin IV 250 mg every 24 h. Follow-up blood cultures were negative. The patient continued these antimicrobial therapies for two weeks, followed by a daptomycin regimen for four more weeks without any adverse effects except for mild stomach discomfort due to gastroesophageal reflux disease. This was verified via upper endoscopy. The kidney function improved five weeks after discontinuing the antimicrobials. One year after discontinuing antimicrobial therapy, the patient's follow-up visit indicated that her general status was healthy without any particular sequelae. Informed consent was provided by the patient for the publication of the Case Report.

Discussion

The 33-year-old woman was successfully treated with daptomycin and levofloxacin for a subacute mitral valve infective endocarditis resulting from the highly penicillin-resistant *Streptococcus mitis/oralis*. There is a paucity of data on the recommended regimen against highly penicillin-resistant VGS.

It is difficult to determine the optimal antimicrobials for infective endocarditis caused by highly resistant VGS, on account of a lack of reported cases; consequently, there are no strong recommendations for highly resistant VGS by either the American Heart Association (AHA)/Infectious Diseases Society of America (IDSA) 2015 or the European Society of Cardiology (ESC) 2015 guidelines.

According to the AHA/IDSA guideline [4], it is recommended to treat patients with infective endocarditis caused by penicillin-resistant VGS (MIC > 0.5 μg/mL) with a combination of ampicillin or penicillin G plus gentamicin (class 2a: level of evidence C). The guideline suggests this recommendation for treating *Enterococcus* sp. as well [4,5]. According to this, alternative regimens for *Enterococci* sp. were linezolid 600 mg administered intravenously or orally every 12 h for more than six weeks (Class 2b; Level of evidence C) or daptomycin 10–12 mg/kg administered intravenously for more than six weeks (Class 2b; Level of evidence C) if the *Enterococcus* species were resistant or intolerant to penicillin, aminoglycoside, or vancomycin.

The ESC 2015 guideline [6], which relies on a retrospective case series, also recommends a treatment regimen for highly resistant VGS, namely penicillin G or ampicillin or ceftriaxone combined with gentamicin for four weeks for native valve endocarditis [6]. This guideline also mentions that vancomycin could be an option, but this is based upon limited evidence. However, in a clinical setting, once acute kidney injury has occurred, continuing aminoglycoside could be difficult, and vancomycin use could be challenging for the maintenance of the appropriate trough level. Both guidelines have limited suggestions on the use of daptomycin.

Daptomycin is a lipopeptide that is bactericidal against a wide range of gram-positive bacterial pathogens, including the antimicrobial-resistant pneumococci, enterococci, and staphylococci. Historically, daptomycin (6 mg/kg daily) was reported not to be inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis [7]. Subsequently, it had been widely used not only for right-sided endocarditis but also for left-sided endocarditis based upon several clinical trials [8]. Although there were few clinical reports related to endocarditis due to highly resistant VGS, in vitro data suggest that outcomes could be improved with higher doses for gram-positive bloodstream infections [9]. Despite daptomycin being a relatively new antimicrobial agent with little data regarding infective endocarditis, it could be an excellent candidate for further clinical trials targeting infective endocarditis due to highly resistant VGS.

The optimal duration of antimicrobials also remains unclear for highly penicillin-resistant VGS. A previous study suggested four- to six-week-long regimens (penicillin plus gentamicin, ceftriaxone plus gentamicin or vancomycin) for infective endocarditis caused by highly resistant VGS [10]. Given that the AHA/IDSA and ESC guidelines recommend a six-week regimen of linezolid or daptomycin for infective endocarditis due to penicillin-resistant enterococci [4], we accordingly continued daptomycin for six weeks. Our patient had been tolerant to daptomycin without any adverse effects, including eosinophilic pneumonia or rhabdomyolysis.

Finally, in the case we describe, we combined levofloxacin with daptomycin for the first two weeks. Although there have been little data concerning the effectiveness of levofloxacin in combination with daptomycin, some studies have reported the efficacy of levofloxacin for the treatment of endocarditis due to VGS [11].

In conclusion, daptomycin could be an alternative to antimicrobial therapy for endocarditis caused by highly penicillin-resistant VGS. Further clinical studies regarding its effectiveness and side effects are warranted.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

TM wrote the manuscript. NM, AS, TK, YM, YU, and KF assisted in the writing the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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