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A Case Report of Penicillin-Tolerant *Streptococcus mitis* Endocarditis

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ABSTRACT

There is no clear relationship between the serum inhibition test and clinical outcome for *Streptococcus mitis (S. mitis)* endocarditis. We report an 84-year-old male with endocarditis caused by penicillin-tolerant *S. mitis*. The results for the serum inhibitory test (SIT) and serum bactericidal test (SBT) showed a trough level of SIT = 1:256 and SBT = 1:4 and a peak level of SIT ≥ 1:1024 and SBT = 1:16. In addition, the SIT/SBT ratio was 64 at peak level and more than 64 at trough level, which is compatible with penicillin-tolerant *S. mitis*. Following a 42-day high-dose penicillin treatment (24 M IU/day, via a continuous drip), the patient made a good recovery. In vitro inhibitory and bactericidal test results were not a valid predictor of medical treatment failure. Physicians need to continue to evaluate the surgical indications when treating patients with *S. mitis* endocarditis.

BACKGROUND

Streptococci and Staphylococci are two common pathogens for infective endocarditis (IE) and are associated with high morbidity and mortality [Vogkou 2016]. The transient viridans streptococcal bacteremia can be induced by minor dental trauma and can be a predisposing factor that causes IE [Baddour 2015]. Among the viridans streptococcus spp., *Streptococcus mitis (S. mitis)* is an extraordinarily adaptable bacterium and commonly causes IE in vulnerable patients.

Historically, penicillin resistance has soon been followed by penicillin tolerance, which always includes resistance to several classes of antibiotics [Pulliam 1979; Habib 2015]. The many reasons for the medical failure of penicillin include the progressive increase of penicillin minimum inhibitory concentrations (MICs) over time, but with values still within the susceptibility range. Habib et al. reported that infections caused by penicillin-tolerant strains are more difficult to eradicate and require antimicrobial regimens with bactericidal activity superior to that of bacteriostatic regimens used in the treatment of serious infectious diseases [Habib 2015]. Penicillin-tolerant *S. mitis* is susceptible, as judged by MICs, but shows an increasing resistance to bactericidal activity, displaying high minimal bactericidal concentrations (MBCs) and an MIC/MBC ratio >32. Bactericidal activity has been regarded as a significant microbiological characteristic in penicillin when treating patients with *S. mitis* IE, while the clinical significance of penicillin tolerance in the treatment of *S. mitis* IE is still unknown.

Here, we report an interesting case of infective endocarditis caused by penicillin-tolerant *S. mitis* in a healthy elderly man. We successfully treated this patient with a high-dose penicillin regimen.

CASE PRESENTATION

An 84-year-old male presented to the hospital with fever and chills, which he had suffered for four hours prior to admission. One month before, he had received an injection in the clinic because of fever, which subsided afterwards. On the current admission, he was sent to the emergency department of our institution. At admission, the laboratory results were as follows: the white blood cell count was 8,700/mm^3 (59% neutrophils, 21% lymphocytes, 11% monocytes, 7% eosinophils, and 2% basophils), the hemoglobin level was 10.7 g/dL, and the platelet count was 25,000/mm^3. Biochemical examinations revealed glutamate-oxaloacetate transaminase levels of 43 U/L, glutamic-pyruvic transaminase levels of 48 U/L, total bilirubin levels of 1.0 mg/dL (direct, 0.3 mg/dL), lactate dehydrogenase levels of 354 U/L, blood urea nitrogen levels of 45 mg/dL, creatinine levels of 1.9 mg/dL, and C-reactive protein levels of 7.0 mg/dL. A plain chest radiograph showed cardiomegaly. Based on these findings, sepsis was suspected, and he was admitted to the infectious diseases ward for further management. On the day of admission, the patient was treated with a 400 mg/day stat dose of teicoplanin plus 2000 mg every 8 hours of ceftazidime for empirical therapy. On day 2 following admission, *S. mitis* was isolated. *S. mitis* was identified with a matrix-assisted laser desorption ionization-time of flight mass spectrometry (bioMerieux, MALDI-TOF MS system, Hazlewood, MO). We performed an antibiotic susceptibility test for *S. mitis* using the bioMérieux VITEK 2 system (bioMerieux, VITEK 2 system, Hazlewood, MO). The results indicated that the *S. mitis* was sensitive to penicillin, ampicillin, ceftriaxone, and vancomycin. The minimum inhibitory concentration values for penicillin is ≤ 0.06 μg/mL. The antibiotics were changed to penicillin G at 3 M units intravenously every 6 hours. Because of a cardiac murmur, we arranged for a cardiac echocardiogram, which revealed vegetation (0.67 X 0.43 cm^2) over the aortic valve. Hence, IE was diagnosed according to Duke's criteria. The penicillin G dose was increased to 3 M units intravenously every 4 hours. A serum inhibitory test (SIT) and serum bactericidal test (SBT)

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were arranged. The results for the SIT and SBT showed a trough level of SIT = 1 :256 and SBT = 1:4 and a peak level of SIT ≥ 1:1024 and SBT =1:16. In addition, the SIT/SBT ratio was 64 at peak level and the SIT/SBT ratio was more than 64 at trough level, which was compatible with penicillin-tolerant *S. mitis*. Because the current dose was insufficient for endocarditis treatment, the dose of penicillin G was adjusted to 24 M IU once daily with continuous a drip. The results for the follow-up SIT and SBT were SIT = 1:128 and SBT = 1:2 at trough level and SIT = 1:1024 and SBT = 1:16 at peak level a week later. The cardiac surgeon suggested that emergent surgery might be needed if the medical treatment failed, but the patient refused the choice of early surgery. During this period, there was no evidence of medical treatment failure, including heart failure and uncontrolled infection. His vital signs stabilized, and he received a full 42-day course of penicillin. He was followed up at an outpatient department, and he was found to have recovered well at the one year follow-up.

DISCUSSION

Although the clinical significance of penicillin tolerance in the treatment of *S. mitis* endocarditis is unknown, it may have important therapeutic implications. This is a case report of penicillin-tolerant *S. mitis* IE in a healthy elderly man. This case report also examines the relationship between penicillin-tolerant IE and clinical therapeutic outcome.

Penicillin tolerance in nutritionally variant *Streptococcus* is characterized by an MBC/MIC ratio of 32 or greater [Richardson 1978]. Holloway and Dankert [Holloway 1982] showed that tolerance to penicillin in nutritionally deficient streptococci could be demonstrated in the presence of pyridoxal, cysteine, penicillinase, and a staphylococcal streak on the subculture medium. However, none of the nutritionally deficient streptococci displayed tolerance when the subculture medium was supplemented with only pyridoxal and cysteine, and various numbers of isolates were tolerant in the presence of other combinations of supplements. If a similar phenomenon occurred in vivo, the physician could face difficulties in treating nutritionally variant *Streptococcus* IE, including *S. mitis* IE. However, Pulliam et al. reported that penicillin tolerance does not appear to be an isolated in vitro phenomenon, although tolerant organisms in cardiac vegetation are killed much less rapidly by penicillin than are non-tolerant organisms [Pulliam 1979]. Careful testing for both the inhibitory and bactericidal action of penicillin might be essential for the successful treatment of *S. mitis* IE. In this case, the results of the SIT and the SBT demonstrated that the inhibitory action of penicillin therapy was adequate, but the lethal action of penicillin therapy was inadequate. We thought that it would be rational to evaluate the effectiveness of penicillin against *S. mitis* by arranging serum inhibitory tests and serum bactericidal tests during the treatment of IE patients. Pasticci et al. showed the rate of tolerance to glycopeptides among Staphylococcal isolates in patients with IE and reported that in vitro bactericidal test results were not valid predictors of clinical outcome [Pasticci 2011]. We thought that the lack of bactericidal activity in vitro could be a reversible phenotypic response due to the growth conditions of the SIT and SBT, and some constitutional changes could be noted in tolerant *S. mitis*. However, in this case report, the in vitro bactericidal test results were not valid predictors of medical treatment failure. We want to emphasize that physicians need to continue evaluating the surgical indications when treating patients with *S. mitis* IE.

The indications for surgery in IE have not changed, although experts in the field have made recommendations based on observational trials and new studies over the decades [Habib 2015]. The indications of surgery in IE could be classified into two major scenarios: heart failure and uncontrolled infection. However, the details are not the same among the guidelines of the European Society of Cardiology [Habib 2015], the American Heart Association, and the American College of Cardiology [Baddour 2015]. Uncontrolled infection is the second most common indication for surgery in IE. Surgery indications include persistent infection, locally uncontrolled infection, and microorganisms with a low likelihood of being controlled by antibiotics. Persistent infection is defined as fever and positive blood culture persisting for 7-10 days after an appropriate antibiotic therapy and an extra-cardiac abscess was excluded. Locally uncontrolled infection includes aortic abscess, fistula, and heart block. The weakest portion of the heart is near the membranous septum and the atrioventricular node, which explains why abscesses occur in this location and why heart block is a frequent sequela. The guidelines from the American Heart Association recommended that transesophageal echocardiography should be repeated at intervals of two, four, and eight weeks after the completion of antibiotic therapy. The guidelines of the American Heart Association and American College of Cardiology recommended surgery in IE caused by fungi or multiresistant organisms (such as methicillin-resistant *S. aureus)*. In contrast, *S. mitis* IE is usually cured by medical therapy alone, even in the case of penicillin-tolerant *S. mitis* IE. We thought that the lack of bactericidal activity in vitro could be reversible in tolerant *S. mitis* and that the in vitro bactericidal test results would not be an accurate predictor of medical treatment failure in this case. Our study provides evidence that physicians should keep in mind when evaluating the surgical indications for patients being treated for *S. mitis* IE.

CONCLUSIONS

This study is a case report of penicillin-tolerant *S. mitis* IE. As a case report, it was difficult to show a significant correlation between penicillin-tolerance and medical treatment failure. In this case, the results of the SIT and SBT were not valid predictors of clinical outcome. We want to emphasize that physicians need to continue to evaluate the surgical indications when treating patients with *S. mitis* IE.

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REFERENCES

Baddour LM, Wilson WR, Bayer AS, et al. 2015. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation 132:1435-1486.

Habib G, Lancellotti P, Antunes MJ, et al. 2015. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 36:3075-3128.

Holloway Y, Dankert J. 1982. Penicillin tolerance in nutritionally variant streptococci. Antimicrob Agents Chemother 22:1073-1075.

Pasticci MB, Moretti A, Stagni G, et al. 2011. Bactericidal activity of oxacillin and glycopeptides against Staphylococcus aureus in patients with endocarditis: looking for a relationship between tolerance and outcome. Ann Clin Microbiol Antimicrob 10:26.

Pulliam L, Inokuchi S, Hadley WK, et al. 1979. Penicillin tolerance in experimental streptococcal endocarditis. Lancet 2:957.

Richardson JV, Karp RB, Kirklin JW, et al. 1978. Treatment of infective endocarditis: a 10-year comparative analysis. Circulation 58:589-597.

Vogkou CT, Vlachogiannis NI, Palaiodimos L, et al. 2016. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. Eur J Clin Microbiol Infect Dis 35: 1227-1245.