CASE REPORT

Successful Treatment of Persistent MRSA Bacteremia using High-dose Daptomycin Combined with Rifampicin

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Abstract

We herein report a case of persistent methicillin-resistant Staphylococcus aureus (MRSA) bacteremia that was successfully treated with combination therapy consisting of high-dose daptomycin (DAP, 10 mg/kg) and rifampicin. The patient’s condition was complicated with multiple infectious foci, including an iliopsoas abscess and epidural abscess, as well as discitis and spondylitis at the cervical, thoracic and lumbar levels. Monotherapy treatments with vancomycin, linezolid and usual-dose DAP were all ineffective. It has been shown that usual-dose DAP administration may result in the emergence of a resistant strain and treatment failure. We would like to emphasize the importance of high-dose DAP therapy for MRSA bacteremia, a condition with a potentially high mortality rate.

Key words: daptomycin (DAP), methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus aureus bacteremia (SAB), butyrylcholinesterase (BChE) deficiency

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Introduction

Staphylococcus aureus bacteremia (SAB) is common in various clinical settings. Persistent bacteremia occurs in 6% to 38% of cases of SAB, and almost half of patients with persistent SAB (>10 days) have secondary lesions (1-3). An advanced age, comorbidities, methicillin resistance and infections with a high bacterial burden have been identified to be risk factors for mortality (4, 5), the rate of which has been reported to vary from 13 to 34% (1, 6-8).

Daptomycin (DAP), a novel cyclic lipopeptide, has a unique bactericidal effect against Gram-positive bacteria, especially methicillin-resistant Staphylococcus aureus (MRSA) (9). In recently published guidelines, the recommended usual dose of DAP for MRSA bacteremia is 6 mg/kg/day (10). However, a recent study demonstrated that usual-dose DAP therapy may not be successful, especially in critically ill patients (11). According to the clinical practice guidelines issued by the Infectious Diseases Society of America (IDSA), the administration of high-dose DAP (10 mg/kg/day or more) in combination with another agent, such as gentamicin, rifampicin (RFP), linezolid (LZD) or trimethoprim-sulfamethoxazole, is recommended in persistent or refractory cases of MRSA bacteremia (10). However, the evidence level for the use of such combination therapy is low (BIII) (10), and the efficacy of this treatment remains controversial.

We would like to express our concern regarding the recommended dose of DAP for MRSA bacteremia by presenting a case of persistent MRSA bacteremia (a total of seven sequential positive blood cultures in 35 days) that could not be controlled with vancomycin (VCM), LZD or usual-dose DAP monotherapy, but rather was successfully treated with a combination of high-dose DAP (10 mg/kg) and RFP.

Case Report

A 78-year-old man (body weight: 50 kg) with a past medical history of total gastrectomy and butyrylcholinesterase (BChE) deficiency was admitted to a hospital due to fever of unknown origin. Prior to symptom onset, he had suffered from cellulitis in the left forearm. Despite the administration of various antibiotics (levofloxacin, piperacil-
Dmia continued, and the patient was transferred to our hospital. The combination therapy was subsequently changed to intravenous linezolid (600 mg every 12 hours). However, the MRSA bacteremia persisted, even after seven days of treatment. Contrast-enhanced magnetic resonance imaging revealed that the left iliopsoas abscess had become smaller; however, multiple areas of discitis/spondylitis (cervical 6/7, thoracic 9/10 and lumbar 4/5) were detected in addition to an epidural abscess at the lumbar level (Fig. 1A). Epidural abscesses were detected at the lumbar level (B; arrows) with multiple areas of discitis and spondylitis (C; cervical 6/7, thoracic 9/10 and lumbar 4/5) on MRI. The multiple infectious lesions were confirmed to have resolved on follow-up MRI performed 18 weeks after treatment (D).

Upon admission to our hospital, the continued presence of MRSA bacteremia was confirmed, despite the administration of DAP. Antimicrobial susceptibility testing showed the MIC of the isolate to be $\leq 0.5 \mu g/mL$ for VCM, $\leq 1.0 \mu g/mL$ for LZD and 1.0 $\mu g/mL$ for DAP. The antibiotic therapy was then changed to DAP at a dose of 350 mg (approximately 10 mg/kg) per day. However, the MRSA bacteremia persisted. The antibiotic therapy was then changed to intravenous linezolid (600 mg every 12 hours). However, the MRSA bacteremia persisted, even after seven days of treatment. Contrast-enhanced magnetic resonance imaging (MRI) revealed that the left iliopsoas abscess had become smaller; however, multiple areas of discitis/spondylitis (cervical 6/7, thoracic 9/10 and lumbar 4/5) were detected in addition to an epidural abscess at the lumbar level (Fig. 1B, C). $^{67}$Gallium-scintigraphy demonstrated uptakes at the same sites (Fig. 2A). Additional surgical intervention was not performed since each abscess cavity was small. A transesophageal echocardiogram was negative for any findings indicating infective endocarditis (IE), and no other intravascular infectious lesions were apparent. By that time, the presence of MRSA bacteremia had been confirmed seven times in 35 days. Combination therapy consisting of high-dose DAP (525 mg per day, approximately 10 mg/kg) and oral RFP (600 mg divided into twice per day) was initiated for the refractory MRSA infection, after obtaining informed consent for the use of high-dose DAP. Only after this treatment was remission of the persistent MRSA bacteremia achieved. Subsequently, the patient’s general condition gradually improved. He was almost bedridden due to debilitation and lumbar pain, but he finally recovered. Eight weeks of the combination therapy was administered without any adverse effects, and he was transferred back to the previous hospital. The combination therapy was subsequently continued, for a total of 18 weeks of treatment. Follow-up MRI (Fig. 1D) and $^{67}$gallium-scintigraphy (Fig. 2B) showed an improvement. Throughout the patient’s clinical course, his renal function was preserved within the normal range; the estimated glomerular filtration rate (eGFR) remained above 80 mL/min/1.73 m$^2$. The clinical course of the present patient is shown in Fig. 3.

**Figure 1.** Multiple abscess formation. CT: computed tomography, MRI: magnetic resonance imaging. A: Contrast-enhanced CT (before drainage). B: Contrast-enhanced MRI (T1-weighted image). C: MRI (Short T1 Inversion Recovery image). D: MRI (Short T1 Inversion Recovery image). A large abscess had formed in the patient’s left iliopsoas muscle (A). Epidural abscesses were detected at the lumbar level (B; arrows) with multiple areas of discitis and spondylitis (C; cervical 6/7, thoracic 9/10 and lumbar 4/5) on MRI. The multiple infectious lesions were confirmed to have resolved on follow-up MRI performed 18 weeks after treatment (D).
Discussion

Persistent bacteremia is generally defined as bacteremia that continues for three to seven days, even with appropriate antibiotic treatment. The risk factors for persistent SAB include infectious foci (i.e., intravascular foci, including IE, mycotic aneurysms, suppurative thrombophlebitis or vertebral osteomyelitis), the bacterial phenotype (drug resistance), the presence of artificial materials, an immunocompromised state and the use of inappropriate treatment (1). The mortality rate for patients with persistent SAB (lasting more than seven days) has been reported to be significantly higher than that for patients with non-persistent SAB (12). The longer the SAB persists, the poorer the outcome (13, 14).

In this report, we describe a case of persistent MRSA bacteremia in which a total of seven positive blood cultures were confirmed despite the administration of VCM (nine days), usual-dose DAP (15 days) and LZD (seven days). Although the patient was free of intravascular lesions, his condition was complicated with multiple infectious foci (left iliopsoas abscess, epidural abscess and cervical, thoracic and lumbar spondylitis). The antecedent infection, cellulitis in the left forearm, was thought to be the entry site of MRSA.

While median the clearance of persistent SAB has been reported to be seven to nine days (1), it was 35 days in this case. It has also been reported that secondary lesions are involved in 45% of cases of SAB persisting for more than 10 days (15, 16), and it is therefore not surprising that our patient was complicated with multiple secondary lesions. A high bacterial load due to the presence of multiple lesions may have been primarily responsible for the refractory course observed in this case. The presence of secondary foci is associated with high rates of recurrence and mortality (17), and both debridement and drainage therapy are essential in such cases. However, except for the iliopsoas abscess, none of the present patient’s lesions were large enough to require additional surgical intervention.

Persistent MRSA bacteremia has a poor prognosis, and particular efforts are needed in such cases. VCM is often used as the first choice of treatment for various MRSA infections (10); however, the application of this agent has decreased due to the emergence of VCM-resistant strains and development of new drugs.

Recently, the incidence of infections due to MRSA with elevated VCM-MIC has been reported to be increasing in association with treatment failure and poor outcomes (18-21). Strains with a VCM-MIC of 2-4 μg/mL had previously been categorized as VCM-sensitive strains, but are now considered to have intermediate susceptibility (22). At present, a VCM-MIC of less than 2 μg/mL is judged to indicate sensitivity; however, even among such strains, higher MIC strains (more than 1 or 1.5 μg/mL) have been increasingly emerging (21, 23-26). This phenomenon of “MIC creeping” has been widely reported (27), and the use of VCM for MRSA strains with such higher MIC values has been demonstrated to be related to treatment failure (24, 28, 29). Therefore, it is essential to perform antibiotic susceptibility testing precisely in laboratories and control the serum concentration of VCM appropriately with therapeutic drug monitoring (TDM). In the present case, the VCM-MIC was not assessed in detail, and the trough level was not controlled properly at the previous hospital; while the target trough level of VCM is considered to be 10 to 20
µg/mL, it was 7.1 µg/mL in our patient. Infections caused by strains with lower VCM-MIC values (less than 0.5 µg/mL) are generally thought to be treatable with VCM; however, treatment with VCM failed in the present case. Apart from the low serum concentration, a high bacterial load due to the presence of multiple lesions may have been responsible for these findings.

In cases of persistent MRSA bacteremia with an elevated VCM-MIC, specialists tend to choose newer drugs, such as LZD and DAP, as alternatives (30). LZD distributes well into various tissues, including bone and muscles, and is recommended as a favorable agent for deep tissue infection caused by MRSA. Jang et al. reported that salvage therapy with LZD is superior to that of VCM for eradicating persistent MRSA bacteremia (31). However, LZD was not effective in our patient. LZD does not penetrate into biofilms (32), which may have been the reason for its ineffectiveness.

Combination therapy using high-dose DAP and RFP was finally effective in the present case. DAP has been shown to be superior to VCM for treating MRSA bloodstream infections when the MIC of VCM is high (more than 1 µg/mL) (33). In our patient, usual-dose DAP (350 mg/day, approximately 7 mg/kg) was initially administered for two weeks; however, the treatment failed. Falcone et al. reported that the pharmacokinetics of DAP can significantly change in patients with sepsis; its clearance is increased and the level of DAP exposure is lower (34). The authors suggested that a minimum of 500 mg or 750 mg of DAP is required to achieve the target concentration (11). Additionally, it has been reported that the incidence of an elevated creatine kinase level, a frequent adverse effect of DAP administration, does not increase with high-dose DAP therapy (11). Although the clinical condition of our patient was relatively stable, he had experienced repeated episodes of bacteremia and his dynamic physiologic state may have been altered. Considering his clinical course, the high-dose DAP was effective.

In the present case, the combined use of RFP may have been effective for the patient’s refractory MRSA bacteremia. RFP has been reported to be effective against biofilm-related MRSA infection in vitro (32). The efficacy of RFP for MRSA osteomyelitis was also recently demonstrated in a clinical systematic review (35), and the long-term use of RFP for such conditions is recommended in recent guidelines (10). The high level of bioavailability of RFP is well accepted, and absorption appears to be maintained, even in gastrectomized patients (36, 37), although these data, which were obtained from a small number of patients 30 years ago, remain inconclusive. Considering the present patient’s clinical course and past history of total gastrectomy, we assume that the treatment effectiveness was obtained not primarily due to RFP, but rather that the combined treatment with high-dose DAP was responsible for the superior outcome.

The unique characteristic of this case was the presence of BChE deficiency. BChE, also known as pseudocholinesterase, hydrolyzes choline esters to choline and organic acid. BChE is synthesized in the liver, and the serum level of BChE is often clinically measured as a parameter of the liver function. However, its mechanism of action in the human body has not yet been elucidated. Hereditary BChE deficiency is a rare condition; however, it is known that patients with the disease have no signs or symptoms, and that there is no association between the condition and an immunocompromised state or infection. Therefore, we consider that the comorbidity of the disease was not related to our patient’s complicated course.

In conclusion, we herein described a case of persistent MRSA bacteremia that was successfully treated with combination therapy consisting of high-dose DAP (10 mg/kg) and RFP. The initial treatment for MRSA infection should be chosen carefully, and the efficacy of high-dose DAP for refractory MRSA infection should be evaluated.

The authors state that they have no Conflict of Interest (COI).

References


