〈CASE REPORT〉

Successful combination therapy with vancomycin and arbekacin against infective endocarditis caused by MRSA

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Infective endocarditis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious disease and sometimes leads to poor prognosis. We should have several therapeutic options. Arbekacin is one of the aminoglycoside antibiotics, which is more active against MRSA and less nephrotoxic than gentamicin. Here we presented a successfully treated case of severe MRSA endocarditis without any adverse effect by monitoring therapeutic level of vancomycin and arbekacin.

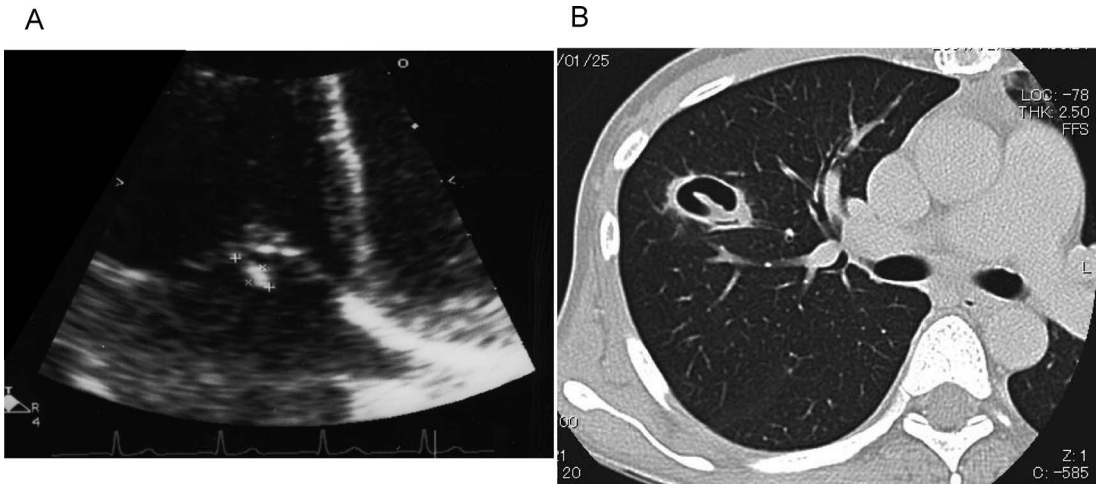
Introduction

Infective endocarditis is a serious disease and sometimes leads to thrombosis and metastatic infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis has a much higher mortality than endocarditis caused by methicillin-susceptible *Staphylococcus aureus* (MSSA)[1]. In spite of aggressive antimicrobial therapy against MRSA, we sometimes experience the treatment failure. We should have several therapeutic options for this severe infection, however the optimal therapy has not been established yet. Here we experienced a successful MRSA infective endocarditis case treated by combination therapy of vancomycin and arbekacin.

Case report

A 38-year-old woman (Ht 160 cm, Wt 45 kg) was admitted to a hospital with a month-long history of high fever, chills, general malaise and leukocytosis. She visited the home doctor and was diagnosed as having upper respiratory infection, however her symptoms did not respond to several short courses of therapy with levofloxacin. She had four teeth removed within one month before the onset. She had also received flu vaccine on the day before the high fever. She had untreated hyperthyroidism but had not been hospitalized nor had a history of drug abuse. A chest X-ray showed multiple cavity formations in the lung fields and several blood cultures were positive for MRSA.

Fig. 1
A: Echocardiogram showed vegetation on tricuspid valve.
B: Chest CT showed cavitary lesion with surrounding inflammation.

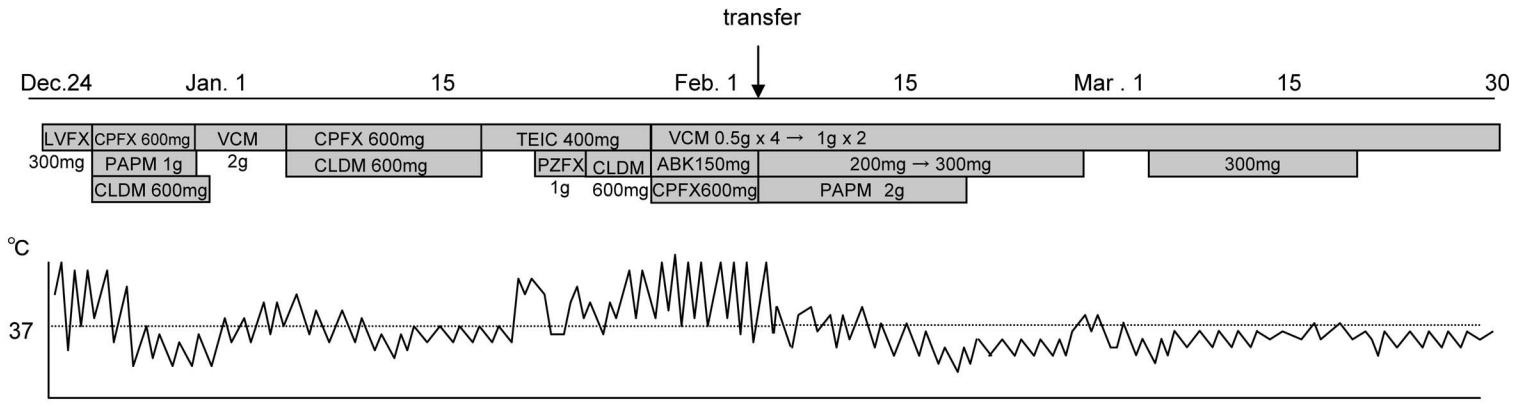


Cultures of bronchoalveolar lavage yielded MRSA and *Candida albicans.* The sensitivity test of MRSA showed sensitive for clindamycin, aminoglycosides, quinolones, vancomycin and teicoplanin. In spite of intravenous antibiotic therapy, including vancomycin, teicoplanin, ciprofloxacin, pazufloxacin and clindamycin, blood cultures were persistently positive for MRSA and finally the third echocardiogram revealed verrucous vegetations affecting the tricuspid valve (Fig. 1A). Disseminated intravascular coagulation (DIC) developed.

On transfer to our hospital, 4/6 holosystolic heart murmur was heard with maximum loudness at the apex. Subcutaneous hemorrhage was observed on bilateral knees. Laboratory examinations revealed a hemoglobin level of 8.3 g/dL, white blood cells count of 1,660/mm^3 and platelets count of 28,000/mm^3. The liver function tests revealed AST of 104 IU/L, ALT of 76 IU/L, ALP of 1,113 IU/L and LDH of 663 IU/L. Thyroid function test revealed a free T4 level of 1.69 ng/dL and TSH level of 0.01 μIU/mL. A chest CT scan revealed multiple cysts and nodules in the right lung field (Fig. 1B). The patient was diagnosed as having MRSA endocarditis with lung abscesses and DIC. Under the administration of vancomycin (0.5 g every 6 h), the trough concentration of vancomycin 5 days after administration in the previous hospital was 5.7 μg/mL. The regimen of vancomycin was changed to 1 g every 12 h and combined with arbekacin (200 mg every 24 h) and panipenem (1 g every 12 h). Through therapeutic drug monitoring (TDM), the trough concentration of vancomycin was increased and maintained from around 15 to 20 μg/mL. As to arbekacin, the dose was increased to 300 mg per day, to raise peak concentration at approximately around 20 μg/mL.

Iodine was given for hyperthyroidism and granulocyte colony stimulating factor was given for

Fig. 2. Clinical course.



Blood culture	MRSA		MSSA		MRSA		MRSA		(−)	(−)		
							Vegetation (+)					
WBC	11,000	3,500	2,700	3,500	8,200	4,300	1,700	1,660	2,350	2,780	2,970	2,160
Plate	10.6	20.1	11.7	14.7	11.4	7.3	4.5	2.8	31.0	18.2	15.4	15.9
CRP	7.12	2.21	1.50	0.22	1.95	2.20	5.50	1.47	<0.06	<0.06	<0.06	<0.06
concentration in serum (μ g/mL)												
VCM trough							5.7	8.4	11.3	19.6	17.7	20.0
ABK peak								10.5	19.7	22.2	19.6	
ABK trough								0.8	1.1	1.3	1.5	

neutropenia for 2 days. Antithrombin III was compensated, and heparin was given for DIC. The patient status improved immediately and panipenem was stopped after 14 days. In total, arbekacin was given for 6 weeks and vancomycin was given for 8 weeks (Fig. 2).

Discussion

Right sided infective endocarditis is usually associated with intravenous drug users and the presence of intravascular catheters or pacemakers. The symptoms of right sided endocarditis are similar to those of respiratory infection. In this case she had received subcutaneous vaccination before the onset, but lacked the common predisposing factors. At the initial phase of this case, there revealed no vegetation on tricuspid valve, which did not fulfill the Duke definite diagnostic criteria. In this case, these facts might lead to the delay of the correct diagnosis. Considering of these characteristics of right sided endocarditis, several reports pointed that the Duke criteria are not appropriate and should be modified[2,3].

Infective endocarditis caused by MRSA is very severe and the outcome is poor. At present, there is no optimal therapy for the disease, and vancomycin has become the standard treatment. However, vancomycin has shown only a bacteriostatic effect on MRSA, which might be one of the reasons for the poor outcome[4]. Several trials of treatments alternative to vancomycin have been performed. Besides, some newer antibiotics have been tried against bacteremia or infective endocarditis caused by MRSA. Linezolid has successfully been used to treat individual cases of MRSA endocarditis[5]. But the long-term safety is questionable because of its suppression of hematopoiesis. In this case, showing thrombocytopenia, it was difficult to use linezolid. Moreover, this drug has shown bacteriostatic effect on MRSA. Daptomycin has recently been proven well tolerated and effective against MRSA bacteremia, including right-sided endocarditis[6,7]. This drug is considered to be bactericidal, however, it is not available in Japan now. Arbekacin is an aminoglycoside antibiotic with antibacterial activity against both Gram-positive and Gram-negative bacteria. It also exerts bactericidal effect on MRSA. But there has not been any report on arbekacin monotherapy for infective endocarditis.

When vancomycin monotherapy fails, combination therapy is the next choice. Combination therapy with vancomycin and gentamicin is recommended in the guideline, based on the fact that this combination showed synergistic effect against the majority of MRSA strains. However, this synergism was not observed with any of the strains highly resistant to gentamicin[8]. Because of the poor susceptibility of MRSA to gentamicin, especially in Japan[9], we could not expect a vancomycin-gentamicin synergism. Arbekacin, unlike other aminoglycosides, is stable in the presence of aminoglycoside-inactivating enzymes produced by MRSA. Moreover, arbekacin showed rapid killing activity against MRSA[10] and the frequency of renal dysfunction is much lower than that observed with gentamicin. *In vitro* studies also showed that arbekacin plus vancomycin exerted a synergistic effect against gentamicin-resistant MRSA[11]. In our patient, several antimicrobial agents were ineffective,

and in the end she was complicated with lung abscesses and DIC. In order to treat such a severe patient, we selected combination therapy with vancomycin and arbekacin. And panipenem was also used during the first 14 days.

The major adverse effects of vancomycin, gentamicin and arbekacin are renal dysfunction and auditory disorder. So extreme caution should be paid, when using these drugs simultaneously. TDM is important to achieve favorable outcome and to avoid adverse reactions[12,13]. Theoretically, the pharmacokinetic-pharmacodynamic (PK/PD) analysis of vancomycin and arbekacin shows that their efficacy depends on the area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) and peak concentration/MIC (Cmax/MIC), respectively. Before this patient was transferred to our hospital, she was administered vancomycin 4 times per day. Unfortunately the concentration was not enough in the previous hospital. Thus we changed the regimen of vancomycin to twice per day and arbekacin to once per day. It is recommended to keep the trough concentration of vancomycin at least 10 to 15 μg/mL. As to arbekacin, it is recommended to keep the peak concentration at around 12 μg/mL and the trough concentration under 2 μg/mL. In a severe situation like this case, the concentration should be kept higher. Therefore, we frequently monitored and raised the trough concentration of vancomycin to around 20 μg/mL and the peak concentration of arbekacin to approximately around 20 μg/mL. Fortunately, our patient suffered no adverse effects. This frequent TDM might be very important to achieve a good outcome and to avoid adverse effects[14].

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