CASE REPORT

Vancomycin Treatment Failure in a Vancomycin Susceptible Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Infected Patient

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SUMMARY

A 64-year old patient, who had bacteraemia, did not respond to vancomycin despite the MRSA isolate being sensitive to the antibiotic at MIC 2µg/mL. Electron microscopy of the MRSA isolate showed thickening of the cell wall, which was not observed in MRSA with lower vancomycin MIC.

KEY WORDS:
MRSA, Vancomycin MIC, Cell wall thickening

INTRODUCTION

Staphylococcus aureus is generally susceptible to vancomycin, however, since 1996 several reports have emerged on its reduced susceptibility. Strains which showed intermediate susceptibility or resistance to vancomycin have been reported in hospitals in Japan, USA and European countries. The vancomycin-intermediate *Staphylococcus aureus* strains (VISA) have minimum inhibitory concentration (MIC) of ≥ 4-8µg/mL, while vancomycin-resistant isolates (VRSA) have MIC ≥ 16µg/mL, based on breakpoints published by Clinical and Laboratory Standards Institute (CLSI). Although the occurrence of these strains is uncommon, therapeutic options for treatment of infections with these strains will be limited.

Susceptible *S. aureus* strains normally have vancomycin MIC values that range between 0.5 and 2µg/mL. Even though methicillin-resistant *Staphylococcus aureus* (MRSA) with vancomycin MIC of 2µg/mL is considered susceptible to vancomycin, treatment failures for strains with this MIC have been reported.

The prevalence of MRSA clinical strains with high vancomycin MICs is not known in Malaysian hospitals. We report here a case of MRSA infected patient who did not respond to vancomycin therapy despite the isolate being susceptible to this antibiotic at the level of 2µg/mL. The cell wall of the MRSA isolate was studied by transmission electron microscopy to determine whether there is any significant difference when compared with a MRSA isolate that has low vancomycin MIC level (0.5 µg/mL).

CASE HISTORY

Patient A was a 64-year-old gentleman, admitted into an intensive care unit after a laparotomy for perforated ulcer. He had persistent fever and blood culture taken on day 17 post-operation, grew MRSA, resistant to erythromycin, gentamicin and co-trimoxazole but sensitive to vancomycin, rifampicin and fusidic acid. Intravenous vancomycin was started but his temperature remained high. A second blood culture taken three days later again grew MRSA with the same antibiotic profile as the first isolate.

A third blood culture taken on day 27 post-operation grew MRSA together with *Klebsiella pneumoniae*. Intravenous vancomycin was terminated and the patient was started on linezolid and meropenem. However, sequential blood cultures taken on days 70 and 75 post-operation still grew MRSA (Table I). Patient succumbed to sepsis on day 85 post-operation.

The MRSA strain isolated on day 27 post-operation was sent to Bacteriology Unit, Institute for Medical Research, for determination of vancomycin MIC.

Antibiotic disc susceptibility tests were carried out using a panel of antibiotics following the CLSI guidelines. MIC was performed using E-test strip (AB Biodisk, Sweden) on Mueller-Hinton agar containing 2% sodium chloride and the agar plate was incubated for 24 hours at 35°C. Screening for VISA was carried out using Brain heart infusion agar containing 6µg/mL vancomycin. The isolate was also sent for transmission electron microscopy of its cell wall at the Electron Microscopy Unit, Institute for Medical Research. A MRSA isolate with vancomycin MIC 0.5µg/mL was also submitted for comparison of the cell wall thickness.

The MRSA strain was found to be resistant to amikacin, gentamicin, erythromycin, ciprofloxacin, tetracycline, co-trimoxazole and rifampicin and sensitive to vancomycin, linezolid, chloramphenicol and clindamycin. The vancomycin MIC was 2µg/mL and is interpreted as sensitive according to the CLSI guidelines. VISA screening test was negative. An increase in the cell wall thickness was noted in this isolate when compared with the MRSA with low vancomycin MIC (Figures 1 and 2) where the cell wall thickness was 48.09 ± 0.87 nm and 26.43 ± 0.25 nm respectively.

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Table I: Days post-operation and bacteria isolated from blood cultures in this patient.

Days post-operation	Specimen taken	Bacteria isolated
Day 17 (12/9/06)	Blood	MRSA
Day 20 (15/9/06)	Blood	MRSA
Day 27 (22/9/06)	Blood	MRSA & *Klebsiella pneumoniae*
Day 65 (30/10/06)	Blood	Mixed growth of 2 types of Gram-positives & 2 types of Gram-negatives.
Day 70 (5/11/06)	Blood	MRSA
Day 75 (10/11/06)	Blood	MRSA & *Pseudomonas aeruginosa* resistant to all antibiotics

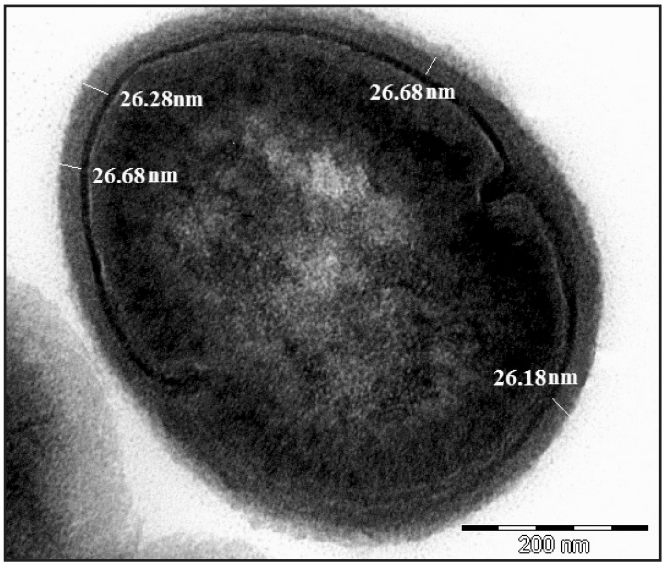

Fig. 1: Transmission electron microscopy of the cell wall of MRSA with MIC 0.5 µg/mL.

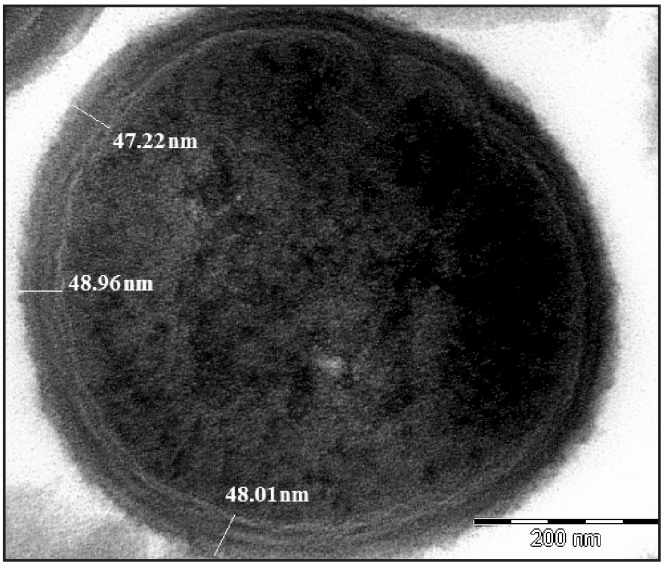

Fig. 2: Transmission microscopy of the cell wall of MRSA with vancomycin MIC 2 µg/mL. Thicker cell wall was noted in this strain compared to Figure 1.

DISCUSSION

Vancomycin is considered the gold standard for treatment of bacteraemia caused by MRSA. In this case, MRSA bacteraemia still persisted even after eight days of vancomycin therapy. Treatment failures against vancomycin susceptible strains have been reported but none looked at the cell wall of the MRSA isolated from these patients.

Vancomycin acts by binding to the D-alanyl-D-alanine residues of murein monomer, thus, inhibiting the peptidoglycan synthesis of *Staphylococcus aureus*. A thicker cell wall will cause more vancomycin molecules to be trapped in the peptidoglycan layers before reaching the cytoplasmic membrane where peptidoglycan synthesis occurs. This will also prevent further penetration by other vancomycin molecules. A thickened cell wall is the cardinal feature of VISA and VRSA strains[1]. However in this case, cell wall thickening was observed in this susceptible isolate of vancomycin MIC 2µg/mL. This implied that greater doses of vancomycin would be needed to overcome the thickened cell wall barrier.

A study by Hidayat *et al* showed that MRSA strains with elevated vancomycin MIC (2 µg/mL) require aggressive empirical vancomycin dosing to achieve a trough greater than 15 µg/mL[2]. The thickened MRSA cell wall as observed in this isolate could also be the reason why a higher trough level needs to be achieved. However, despite achieving the target trough, the patients in this MIC group (2µg/mL) had lower end-of-treatment responses and higher infection-related mortality compared with the low-MIC group (< 2 µg/mL).

A combined or alternative treatment should be considered when faced with MRSA with this MIC value. Patients who were switched to a non-vancomycin therapy were shown to respond favourably but failed treatment did occur in some cases[2]. Linezolid is not licensed for treatment of *S. aureus* bacteraemia while daptomycin showed a higher success rate than vancomycin plus gentamicin, although the difference is not significant[3].

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