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CASE REPORT

Emergence of a strain of methicillin-resistant *Staphylococcus aureus* with decreased susceptibility to vancomycin 7 months after treatment with glycopeptide antibiotics

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This case report describes a methicillin-resistant *Staphylococcus aureus* isolated repeatedly from the blood of a patient with community-acquired endocarditis who developed a four-fold increase in the minimal inhibitory concentration of vancomycin and daptomycin 7 months after his last exposure to glycopeptide antibiotics. This is contrary to the expected situation in which antimicrobial resistance tends to decrease after a patient is no longer exposed to vancomycin.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the 1960s,[1] and gradually became an endemic pathogen in hospital settings in the 1980s. This led to the extensive use of vancomycin for the treatment of MRSA infections. MRSA with reduced vancomycin susceptibility

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appeared in the 1990s, and tends to disappear following cessation of vancomycin therapy.[2] The current report describes a strain of MRSA, repeatedly isolated from the blood of a patient with community-acquired bacterial endocarditis, which exhibited a delayed increase in the minimum inhibition concentration (MIC) of vancomycin 200 days following treatment with vancomycin and teicoplanin.

Case report

A 45-year-old male intravenous drug user was admitted to Kaohsiung Veterans General Hospital, Taiwan in March, 2007 with MRSA infective endocarditis and lumbar spine osteomyelitis. He was treated with vancomycin for 3 days followed by a 24-day, intermittent course of teicoplanin. During this period, the MIC of vancomycin rose from 2 mg/dL to 4 mg/dL. Teicoplanin was switched to linezolid on Day 19 due to persistence of fever. There were no glycopeptide exposures since then. Blood cultures were obtained as an outpatient at 1–3 week intervals. MRSA was re-isolated on the Day 110. He was treated for 110 days with oral trimethoprim–sulfamethoxazole and chloramphenicol. He was readmitted on the Day 257 because of fever. MRSA with an MIC of 8 mg/dL was isolated from his blood. There was no concurrent infection with vancomycin-resistant enterococci. He was treated with linezolid and chloramphenicol for 23 days and then switched to trimethoprim–sulfamethoxazole and moxifloxacin until Day 337. Blood cultures continued to remain sterile after Day 264. The patient was not screened for colonization with MRSA or vancomycin-resistant enterococci. A preliminary report of this case was published[3] prior to noting the four-fold rise in the MIC of vancomycin and daptomycin on Day 257 and knowledge of the follow-up by Day 110 day.

Laboratory studies

Blood culture isolates obtained at Day 0, Day 47, Day 55, Day 110, and Day 257 were stored at −80°C. Following reconstitution antibiotic susceptibility and genetic profiles were performed on all the isolates together with *S. aureus* ATCC 29213. The MICs for vancomycin, daptomycin, rifampin, gentamicin, trimethoprim–sulfamethoxazole, and moxifloxacin were determined, in duplicate, by broth microdilution using Sensititre custom designed plates for staphylococci (Trek Diagnostics, East Grinstead, West Sussex, UK). The MIC for teicoplanin was determined by the E-test (AB Biodisk, bioMérieux SA, Marcy l'Etoile, France). Pulsed field gel electrophoresis (PFGE) was conducted using standard DNA extraction methods. Lambda ladder PFG marker (New England Biolabs, Schwalbach, Germany) was used as fragment size marker. The type IV staphylococcal cassette chromosome *mec* and Panton–leukocidin genes were determined as previously described.[3] Multilocus sequence typing (MLST) was performed as described by Enright et al.[4] The MLST sequences were submitted to the MLST database (http://www.mlst.net/). Spa typing was performed using methods described by Harmsen et al.[5]

The antimicrobial susceptibility results are shown in Fig. 1. The key findings were a four-fold increase in the MICs of vancomycin, teicoplanin, and daptomycin without significant changes in the MICs of the other antibiotics during the study period. All isolates were found to be identical by

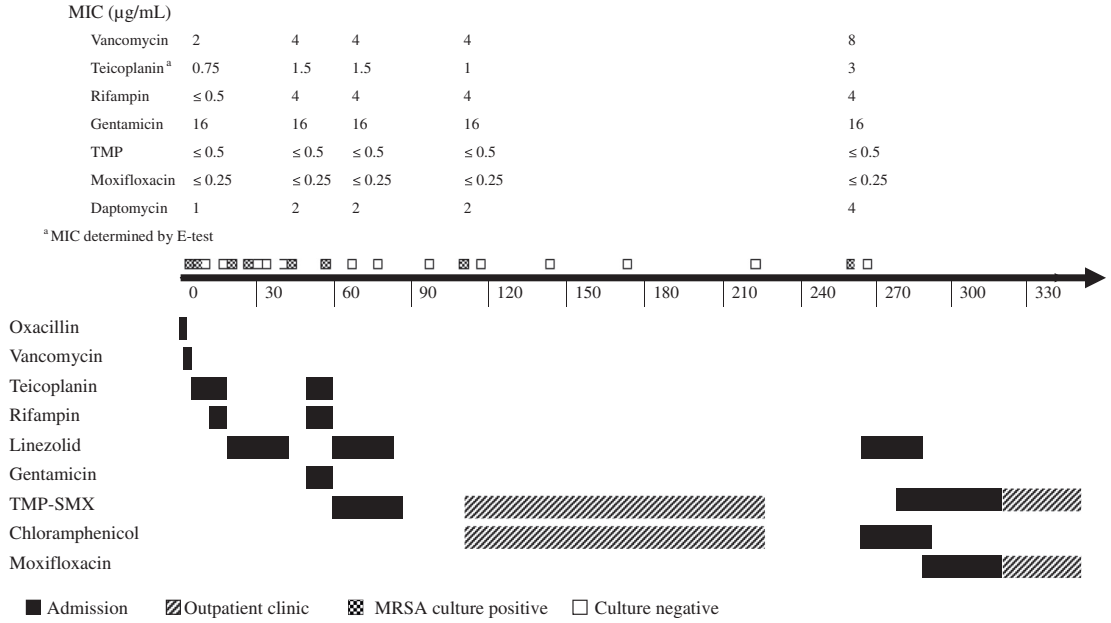

Figure 1. Course of treatment of a patient with bacterial endocarditis in Taiwan with the minimal inhibitory concentrations (MICs/dL) to 10 antibiotics of a methicillin-resistant strain of *Staphylococcus aureus* repeatedly isolated from his blood during March–November 2007. MIC determined by the E-test method. MRSA = methicillin-resistant *Staphylococcus aureus*; TMP-SMX = trimethoprim–sulfamethoxazole.

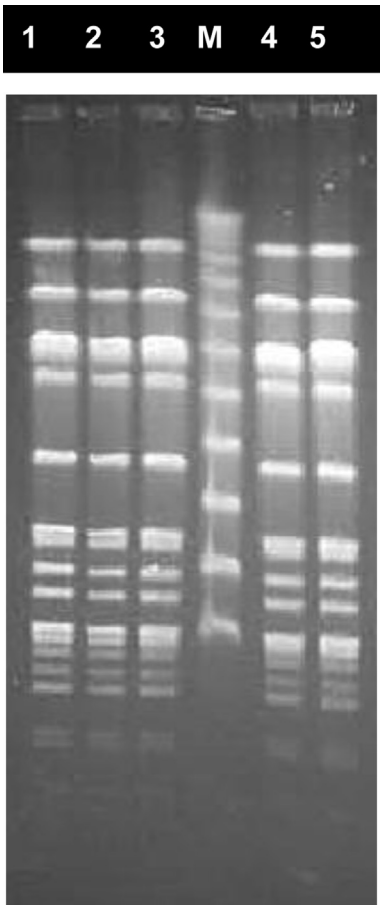

Figure 2. Pulsed-field gel electrophoresis patterns of methicillin-resistant *Staphylococcus aureus* isolated from the blood of a patient with bacterial endocarditis (Isolates 1—5). Lane M = lambda ladder pulsed-field gel marker.

PFGE typing (Fig. 2). The isolate contained the type IV staphylococcal cassette chromosome *mec*, Panton—leukocidin genes, ST type 59, and *spa* type t437.

Discussion

Decreased susceptibility to vancomycin following prolonged exposure to subinhibitory concentrations is attributed to the development of tolerance and decreased autolysis.[6,7] MRSA strains tend to lose resistant subpopulations after a week of serial passage in a drug-free media.[3] Our patient received vancomycin for 3-days and teicoplanin for 24 days. Nevertheless, the MICs of vancomycin, teicoplanin, and daptomycin continued to rise up to 254 days after the last dose of vancomycin and almost 200 days after the last exposure to teicoplanin. He was followed-up regularly in the outpatient department and was exposed only to linezolid, chloramphenicol, and trimethoprim—sulfamethoxazole. Vancomycin trough level assays were not available at our institution during the time of the study. The PFGE and genetic studies provide strong evidence of clonal identity of all the isolates. Thus the phenomenon cannot be explained by superinfection with new strains of MRSA.

Prolonged exposure to teicoplanin appears to be the most likely explanation for the reduced susceptibility to vancomycin. Shlaes and Shlaes[8] demonstrated that vancomycin-resistant MRSA mutant may appear after exposure to another glycopeptide. An unexpected finding was the sequential increase in resistance to daptomycin after a remote exposure to glycopeptides. A relationship between resistance to daptomycin and vancomycin has been described.[9] It has been postulated that the thickened wall of vancomycin-intermediate *S. aureus* may impede the access of daptomycin to the cell membrane surface.[10] The combined increase in resistance to glycopeptides and daptomycin after remote exposure to vancomycin has not, to our knowledge, been previously described. A reversion of resistance is generally expected after removal of the selecting agent; this case demonstrates that persistence of resistant clones with paradoxical progression of resistance is possible, and is a reason for concern. It is not known whether exposure to other antistaphylococcal antibiotics may have played a role.

Conflicts of interest

All contributing authors declare no conflict of interest.

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