Enterococcus faecium with High Level Vancomycin Resistance Isolated from the Blood Culture of a Bone Marrow Transplant Patient in Malaysia

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Summary

Since 1988 vancomycin-resistant enterococci have been described in North America and Europe but not in Asia. We report the isolation of a strain of *Enterococcus faecium* showing high-level resistance to vancomycin (MIC > 256 mg/l) from the blood culture of a 21-year-old bone marrow transplant patient in Malaysia.

Key Words: Vancomycin resistance, *Enterococcus faecium*, Antibiotic resistance

Introduction

Since its introduction in the 1950s, the glycopeptide antibiotic vancomycin has been vitally important in the treatment of infections caused by Gram-positive bacteria resistant to beta-lactams and other agents. Such organisms include methicillin-resistant *Staphylococcus aureus,* penicillin-resistant *Streptococcus pneumoniae* and ampicillin-resistant enterococci. Vancomycin also has a role in the treatment of infections in patients who are allergic to other antibacterial agents.

Clinically significant infections caused by vancomycin-resistant enterococci were first reported in 1988[1] and subsequently there have been many reports of vancomycin-resistant enterococci from Europe and North America, but not from Asia[2]. We now describe the isolation of a vancomycin-resistant *Enterococcus faecium* from the blood culture of a bone marrow transplant patient in Malaysia.

Case Report

A 21-year-old man from Sabah with severe aplastic anaemia of one year's duration was admitted to the University Hospital, Kuala Lumpur for bone marrow transplantation. Prior to this he had spent several months as an inpatient in other hospitals and had received multiple courses of antibiotics. A Hickman catheter was inserted and pre-transplant conditioning, including prophylactic norfloxacin and co-trimoxazole, was commenced. Bone marrow transplant was performed twelve days later and co-trimoxazole was stopped. Norfloxacin was continued until 21 days post-transplant.

The patient remained profoundly neutropenic and had several febrile episodes over the ensuing weeks. Proven Gram-negative bacteraemia occurred on three occasions with *Acinetobacter* sp., *Citrobacter freundii* and *Stenotrophomonas maltophilia,* for which he received appropriate antibiotics which included ceftazidime, ciprofloxacin and imipenem. He had several other febrile episodes during which no organisms were isolated from blood cultures and on these occasions he was treated empirically with antibiotics including ceftazidime, imipenem and vancomycin. Twenty-one days post-transplant bilineage engraftment was demonstrated, but on day 54 it was concluded that

the bone marrow transplant had been rejected. He was subsequently commenced on conditioning therapy for a second transplant.

Seventy-eight days after the first transplant the patient was febrile again and aerobic and anaerobic blood cultures were performed on blood samples drawn via both the large and small lumens of the Hickman line. He was started empirically on vancomycin. The following day chaining Gram-positive cocci, identified as *Enterococcus faecium*, by their API 20 Strep profile (bioMérieux, 69280 Marcy-l'Etoile, France) were isolated in the aerobic culture of blood taken via the large lumen of the Hickman line. Two different strains of *E. faecium* were present; a vancomycin sensitive strain with an MIC of 0.5 mg/l by E test (AB Biodisk, Pyramidvägen 7, S-17136 Solna, Sweden) and a vancomycin resistant strain with an MIC > 256 mg/l by E test. Both strains were resistant to ampicillin, co-amoxiclav, erythromycin, tetracycline, chloramphenicol, co-trimoxazole, rifampicin and showed intermediate susceptibility to ciprofloxacin by disc diffusion tests. Vancomycin resistant *E. faecium* was isolated from a rectal swab taken from the patient. Despite the vancomycin resistance, the patient became afebrile and the vancomycin was stopped after three days. The blood cultures drawn via the small lumen of the Hickman line remained sterile. Repeat blood cultures taken via a peripheral vein and via the Hickman line remained sterile.

Discussion

Vancomycin has been in use since the 1950s but unlike many other antibiotics, clinically significant bacterial resistance has been comparatively slow to develop and vancomycin continued to have an important place in the treatment of infections caused by Gram-positive organisms resistant to beta-lactams and other agents. Although enterococci are organisms of low virulence, they have emerged as important hospital pathogens probably due to the selective pressure resulting from the high use of cephalosporins, to which enterococci are naturally resistant. Coupled with an ever increasing use of vancomycin, the eventual development of vancomycin resistance was the nemesis for which all clinical microbiologists were waiting and in 1988 the first cases were described[1]. Subsequently there were many other reports from Europe and North America, but interestingly no cases described in Asia[2]. Several phenotypic variants of vancomycin resistant enterococci have been described and these are based on the degree of resistance as judged by the MICs of vancomycin and the related glycopeptide teicoplanin[2]. The strain described in this paper displayed high level resistance and is consistent with the VanA phenotype. Strains with low level vancomycin resistance are usually susceptible to teicoplanin and are designated as the VanB phenotype. Two further low-level resistance phenotypes designated VanC-1 and VanC-2 have also been described. Vancomycin resistance may be either plasmid-mediated or chromosomal. A discussion of the genetic and biochemical basis of vancomycin resistance is beyond the scope of this case report but it has been comprehensively reviewed elsewhere[2].

Blood stream infections with vancomycin-resistant enterococci are still relatively unusual in North America and Europe where many of the patients are colonised rather than infected. Risk factors strongly implicated in the development of blood stream infection include haematologic malignancy, bone marrow transplantation and the receipt of vancomycin[3], two of these factors being present in our patient.

The case described in our paper illustrates the major dilemma posed by vancomycin-resistant enterococci – how to treat the patient? The vancomycin-resistant isolate was resistant to all other antibiotics tested with the exception of ciprofloxacin to which intermediate susceptibility was demonstrated, but clinical experience with this antibiotic has not been very encouraging and it is probably only effective in the treatment of urinary tract infections[2]. Antibiotics such as the lipopeptide daptomycin and some of the pristinamycins have shown impressive in vitro activity but their clinical efficacy has yet to be fully elucidated. In some situations the synergistic use of triple combination therapy with ampicillin, vancomycin and gentamicin has been effective, but this combination is not indicated when high-level gentamicin resistance is present[2]. It is important to distinguish between true infection and colonisation and it is likely that in our patient there was colonisation of the Hickman catheter rather than true bacteraemia. This may account for the apparent response to vancomycin therapy despite

the high level resistance. Removal of infected intravenous devices or other prosthesis must be considered and may be the only treatment available.

Infection control implications must not be overlooked and in our case it was fortunate that the patient was nursed in isolation since his admission for the bone marrow transplant. It remains to be seen whether standard infection control procedures will be sufficient to prevent spread of vancomycin-resistant enterococci. A review of the current use of vancomycin and cephalosporins may also need consideration.

References

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Intra-Abdominal Desmoplastic Small Round-Cell Tumour: Response to Multimodality Treatment

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Summary

A Malaysian case of this recently-described aggressive tumour is reported. A 16-year-old Malay boy presented with a large abdominal mass and iron deficiency anaemia. After incomplete resection of the mass at laparotomy, the residual disease showed response to chemotherapy. However, 'second-look laparotomy' showed nodules of residual disease in the liver. He underwent further chemotherapy and total abdominal radiotherapy. The patient remained in remission for 6 months, but relapsed and died 30 months after diagnosis. This tumour is responsive to aggressive multimodality therapy, but most patients die of their disease.

Key Words: Abdominal neoplasm, Combined modality therapy, Desmoplastic, Small cell tumour