Case Report

Active Surveillance Revealing an Underlying Nosocomial Outbreak of Vancomycin-Resistant Enterococcus faecium in a Tokyo Hospital

Tomoki Watanabe1,2, Ryoko Adachi1, Manami Takahashi1, Emi Kuroda1, Kayo Shimada3, Takahiro Nomura4, Kazuhisa Mezaki5, Keishiro Izumi1, Haruyoshi Tomita5, Teruo Kirikae4* and Yasuyuki Kato7

1Department of Pharmacy, National Center for Global Health and Medicine, Japan
2Department of Drug Information, Showa University, Japan
3Department of Nursing, National Center for Global Health and Medicine, Japan
4Department of Infectious Diseases, National Center for Global Health and Medicine, Japan
5Department of Bacteriology and Bacterial Infection Control, Gunma University Graduate School of Medicine, Japan
6Department of Microbiology, National Center for Global Health and Medicine, Japan
7Department of Disease Control and Prevention Center, National Center for Global Health and Medicine, Japan

Abstract

Vancomycin-resistant Enterococcus faecium NCGM16 was isolated 59 days after the transfer of a patient from a hospital in the United States to a hospital in Tokyo. Vancomycin-resistant enterococci (VRE) had not been isolated at the U.S. hospital, and the patient was not screened for VRE upon admission to the hospital in Tokyo. Patients at the latter hospital were actively screened for VRE to determine if a VRE outbreak had occurred. The surveillance detected three other VRE carriers. The VRE isolates (NCGM17, 18, and 20) from these three carriers were identical to each other in drug susceptibility profiles, patterns on pulsed-field gel electrophoresis and multi locus sequence types, but differed from NCGM16. NCGM16 and 17 had different types of Tn1546-like elements containing van A. These molecular epidemiology results indicate that an underlying outbreak of VRE had occurred when the transferred patient was in the Tokyo hospital but that NCGM16 did not cause an outbreak in that hospital. Restricted infection control measures were performed during the outbreak. Active surveillance for VRE and molecular epidemiology are useful in detecting VRE outbreaks.

ABBREVIATIONS

CC: Clonal Complex; ICT: Infection Control Team; MLST: Multi locus Sequence Typing; PFGE: Pulsed-Field Gel Electrophoresis; ST: Sequence Type; VRE: Vancomycin-Resistant Enterococci

INTRODUCTION

Vancomycin-resistant enterococci (VRE) are spreading in medical settings worldwide [1]. A national surveillance in Japan (http://idsc.nih.go.jp/idwr/ydata/report-Ea.html) determined that 120 patients were infected with VRE in 2010, prevalence lower than in the United States.

VRE are transmitted through direct contact with colonized or infected patients, or through indirect contact via the hands of health care workers, medical equipment, or environmental surfaces [2]. Active surveillance cultures are essential to identify reservoirs for spread of VRE infections [3].

This report describes an underlying VRE outbreak in a hospital in Tokyo, in which active surveillance revealed the
outbreak after a patient carrying VRE was transferred from the United States, a country with a higher prevalence of VRE.

CASE PRESENTATION

A 50-year-old Japanese man (Patient 1) was transferred from a hospital in Los Angeles, California, to a hospital in Tokyo. He had been diagnosed with rectal cancer accompanied by liver metastases and rectovesical fistulae. The report from the hospital in Los Angeles did not mention VRE isolation. The patient was transferred to a hospital with 750 beds in Tokyo and hospitalized there for 49 days to undergo chemotherapy with fluorouracil, leucovorin and oxaliplatin. After discharge, he had fever and was hospitalized again on 56 days after the first admission.

He was not screened for VRE at the time of first admission. At readmission on day 56, a urine sample was sent to a microbiological laboratory due to suspected urinary tract infection. Vancomycin-resistant Enterococcus faecium was isolated from the sample on day 59. He was treated with linezolid but died of the cancer on day 210.

The microbiology laboratory reported isolating VRE from the patient to the Infection Control Team (ICT), which is in charge of implementing infection control activities in the hospital. The ICT assumed that the VRE isolate had come with the patient from the United States for several reasons. First, the patient had been transferred from a country with a high VRE prevalence (the United States) to a country with a low VRE prevalence (Japan). Second, only two VRE-infected patients or VRE carriers had been identified and no VRE outbreak had occurred in the Tokyo hospital since 2002 when the ICT began its activities. However, several VRE isolates were obtained from different patients in another hospital in Tokyo [4].

The hospital ICT initiated active surveillance for VRE by collecting stool samples or rectal swabs for 152 days, from patients treated during the same periods and in the same wards as Patient A and from suspected VRE carriers, regardless of whether they were hospitalized or followed up in the outpatient department. VR-EF agar plates (Nissui Pharmaceutical, Tokyo, Japan) were used to screen for VRE. A total of 1961 patients, including 180 possible contacts, were screened during the surveillance. Three VRE carriers (Patients B, C, and D) were identified. Patient B was a 73-year-old Japanese man hospitalized to undergo total gastrectomy for gastric cancer; Patient C was a 73-year-old Japanese man with colon cancer hospitalized for treatment of ileus, and Patient D was an 80-year-old Japanese man hospitalized for treatment of hepatic abscess. Patient A and the three VRE carriers were hospitalized during overlapping periods in the same ward. The estimated cost of contact isolation precautions, including extra fees for a bed in a single room, personal protective equipment, and bacterial examinations, was at least 6,684 USD.

Bacterial species and MICs of antibiotics were determined using MicroScan WalkAway™ (Siemens Healthcare Diagnostics, Tokyo, Japan) and the micro dilution method, according to the guidelines of the Clinical and Laboratory Standards Institute. PCR was performed to determine the presence of \( \text{vanA}, \text{vanB}, \text{vanC1} \) and \( \text{vanC2} \); and pulsed-field gel electrophoresis (PFGE) analysis and multilocus sequence typing (MLST) of E. faecium and the DNA sequences of the Tn1546-like elements were determined as described [5].

All four VRE isolates obtained from patients A–D were resistant to vancomycin and teicoplanin with MICs of 128–512 \( \mu \text{g/mL} \) and 128 \( \mu \text{g/mL} \) respectively. The drug susceptibility profile of the isolate from patient A (NCGM16) differed from those of the three isolates from patients B–D (NCGM17, 18, and 20, respectively). The profiles of the latter three isolates were similar to each other, with MICs of gentamicin, streptomycin, and tetracycline being >1024 \( \mu \text{g/mL} \), 64 \( \mu \text{g/mL} \), and 0.125 \( \mu \text{g/mL} \), respectively, compared with 8 \( \mu \text{g/mL} \), >1024 \( \mu \text{g/mL} \), and 64 \( \mu \text{g/mL} \), respectively, for NCGM16 (Table 1). All four isolates harbored \( \text{vanA} \) (data not shown). The PFGE patterns of NCGM16 differed from those of the other three isolates, although the patterns of NCGM17, 18, and 20 were identical to each other (Figure 1). NCGM16 belongs to sequence type (ST) 584, a variant of ST17, whereas the other three isolates belong to ST203. Both ST584 and ST203 belong to clonal complex (CC) 17, which has spread globally [6]. The genetic environments surrounding \( \text{vanA} \) in NCGM16 and NCGM17 differed (Figure 2). NCGM16 and NCGM17 had different types of Tn1546-like elements containing \( \text{vanA} \). Tn1546 of NCGM16 had three characteristic genetic structures: an IS1216V insertion in a non-coding region 736bp downstream of ORF1, resulting in the deletion of the 890bp downstream region; an IS1251-like insertion in an intergenic region between \( \text{vanS} \) and \( \text{vanR} \); and an IS1216V insertion in an intergenic region between \( \text{vanX} \) and \( \text{vanY} \). The genetic structure of Tn1546 of NCGM16 was similar to that of Tn1546 type F1, which was shown to have the IS1216V insertion in the region downstream of the deleted ORF1 and the IS1251-like insertion, but not the IS1216V insertion between \( \text{vanX} \) and \( \text{vanY} \) [7]. A VRE carrying Tn1546 type F1 was isolated in Chicago, Illinois, in the United States [7]. Tn1546 of NCGM17 had the IS256 insertion into a non-coding region 62 bp upstream of \( \text{vanB} \), but did not have the IS1216V or IS1251-like insertion. Additionally, \( \text{vanX} \) and \( \text{vanY} \) of NCGM17 had mutations at 8255bp and 9692bp, respectively. A VRE carrying this type of Tn1546 was recently isolated in Okinawa, Japan, and the details will be reported elsewhere.

DISCUSSION

Active surveillance of VRE and molecular epidemiology are useful to detect VRE outbreaks. Once VRE outbreaks occur in hospitals in regions with low prevalence of VRE, these hospitals must make enormous efforts to control the outbreaks, including intensive active surveillance to detect VRE carriers and isolation of patients infected with or carrying VRE. It has been
Table 1: VanA-type vancomycin-resistant *E. faecium* clinical isolates.

| Strain  | Source | MIC (µg/ml) | VAN | TEC | AMP | GEN | STR | TET | ERY | CHL | RIF | LVX | LZD |
|---------|--------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| NCGM16  | Urine  | 512         | 128 | 256 | 8   | >1024| 64  | 1024| 8   | 4   | 256 | 2   |
| NCGM17  | Stool  | 256         | 128 | 256 | >1024| 64  | 0.125| 1024| 8   | 8   | 256 | 2   |
| NCGM18  | Stool  | 128         | 128 | 256 | >1024| 64  | 0.125| 1024| 8   | 8   | 256 | 2   |
| NCGM20  | Stool  | 256         | 128 | 256 | >1024| 64  | 0.125| 1024| 8   | 8   | 256 | 2   |

**Abbreviations**: VAN: Vancomycin; TEC: Teicoplanin; AMP: Ampicillin; GEN: Gentamicin; STR: Streptomycin; TET: Tetracycline; ERY: Erythromycin; CHL: Chloramphenicol; RIF: Rifampicin; LVX: Levofloxacin; LZD: Linezolid.

Figure 2 Genetic organization and typing of Tn1546-like elements found in Tokyo clinical isolates. The genetic structure of the prototype of Tn1546 type A1 is shown [7]. White boxes show the genes and open reading frames (ORFs) encoded on the prototype Tn1546 element. Dotted boxes represent IS elements. Filled arrows indicate the transcriptional orientation of the inserted IS elements. The numbers at the IS insertions show the positions of the first nucleotides upstream and downstream of the inserts. The horizontal arrows on the IS elements indicate the transcriptional orientation of the transposase encoded on the ISs.

---

recommended that all patients admitted to units that care for patients at high risk of hospital-acquired infection be screened for VRE [8].

Screening not only for VRE but for other drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenemase- and extended-spectrum β-lactamase-producing gram-negative bacteria, will be necessary upon admission of patients transferred from abroad [9]. Several case reports have described the isolation of multidrug-resistant bacteria, such as OXA-48 carbapenemase-producing *Klebsiella pneumoniae*, from a traveler returning from a foreign country to Japan [10].

The present results indicated that there was a possibility of an underlying outbreak of VRE when the patient from Los Angeles was in the Tokyo hospital but that NCGM16 had not been transmitted to other patients in the hospital.

**ACKNOWLEDGMENTS**

The study was approved by Human Research Ethics Committee of National Center for Global Health and Medicine (NCGM/G/001449/00).

**Conflict of Interest**

This study was supported by a grant from the Agency for Medical Research and Development of Japan.

**REFERENCES**


