Case Report / *Olgu Sunumu*

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Enterococcus Casseliflavus Bacteremia: A Report of Two Cases and Review of the Literature

Enterococcus Casseliflavus Bakteriyemisi, İki Olgu ve Literatürün Gözden Geçirilmesi

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Abstract

Intrinsically vancomycin-resistant Enterococci are rarely recovered from blood culture. These microorganisms usually exist in human gastrointestinal tract. Enterococci have an important role in serious invasive infections, including nosocomial infections, endocarditis, bacteremia, urinary tract infection, and pelvic infection. The clinical importance of intrinsically vancomycin-resistant enterococci is increasing day by day, because some of them are responsible for recurrent bacteremia in humans with malignancy and receipt of transplant history. Generally, intrinsic low-level vancomycin resistance (vanC type) is observed in *E. casseliflavus* and *E. gallinarum* species. However, *E. gallinarum* isolates which carried both the vanC1 and vanA genes were described in two research. In our study, we reviewed the medical records of two patients with *E. casseliflavus* bacteremia and investigated underlying diseases or conditions. Both patients had chronic renal failure and they were being treated in the hemodialysis unit at our hospital. When reproduction was detected in their blood culture, the patients were administered combination therapy including daptomycin+imipenem and daptomycin+cefepime during bacteremia periods. The patients' condition improved within 72 hours with treatment. In conclusion, this study demonstrates that intrinsically vancomycin-resistant enterococci have the clinical significance in the treatment of in bacteremia developing on basis of a chronic illness or malignancy. *(The Medical Bulletin of Haseki 2015; 53: 175-8)*

Key Words: *E. casseliflavus*, intrinsic low level vancomycin resistance, bacteremia

Özet

İntrensek vankomisin dirençli olan enterokoklar kan kültürlerinden nadiren izole edilirler. Bu bakteriler insan ve hayvanların gastrointestinal sistemlerinde bulunurlar. Enterokoklar endokardit, bakteriyemi, üriner ve pelvik enfeksiyonları kapsayan ciddi invaziv enfeksiyonlarda önemli role sahiptir. İntrensek vankomisin dirençli enterokokların klinik önemi gün geçtikçe artmaktadır. Çünkü bunlardan bazıları altta yatan malignite ve transplantasyon öyküsüne sahip hastalarda, tekrarlayan bakteriyemilerin sorumlusudur. *E. casseliflavus* ve *E. gallinarum* türlerinde genellikle düşük düzey intrensek vankomisin direnci (vanC tip) bildirilmektedir. Ancak iki araştırmada vanC1 ve vanA genlerini birlikte taşıyan *E. gallinarum* izolatları tanımlanmıştır. Çalışmamızda, *E. casseliflavus* bakteriyemisi olan iki hastaya ait bulgular ve altta yatan hastalıkların incelenmesi amaçlanmıştır. Her iki hasta da kronik böbrek yetmezliği olan ve hastanemizde dializ tedavisi gören hastalardır. Kan kültürlerinde üreme saptandığında hastalara daptomisin+imipenem ve daptomisin+sefepim kombinasyon tedavileri verilmiştir. Hastaların genel durumu 72 saat içinde düzelmiştir. Sonuç olarak, malignite ve kronik hastalık zemininde gelişen bakteriyemilerde intrensek vankomisin dirençli enterokokların tedavisinin önemine dikkat çekmek gerekmektedir. *(Haseki Tıp Bülteni 2015; 53: 175-8)*

Anahtar Sözcükler: *E. casseliflavus*, intrensek düşük düzey vankomisin direnci, bakteriyemi

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Introduction

It is known that Enterococci colonize the genitourinary system, biliary tract and the, oral cavity as a normal flora bacteria in human gastrointestinal system (1). However, the tendency to Enterococcal infections is observed in patients with immune deficiency and in those, receiving long-term hospital care or previously used intensive dose of antibiotics (2). In recent years, vancomycin-resistant roots of Enterococcal infections became one of the most important causes of nosocomial infections (3).

Enterococci are bacteria in the form of single, in pairs or short chains. Also, *Enterococcus*, caralase-negative, facultative anaerobes, are the bacteria growing in a media that contains 9.6 pH, 40% bile salt. In sheep blood agar, *Enterococcus* colonies are sizable, gray and bright, plus alpha, beta hemolytic or non-hemolytic. The types, except for *Enterococcus* cecorum, *Enterococcus* columbae and *Enterococcus* saccharolyticus hydrolyze the substance pyrrolidonyl arylamidase. Some of the types like *Enterococcus* flavescens, *Enterococcus* casseliflavus and *Enterococcus* gallinarum are mobile. There are two types of vancomycin resistance in enterococci. The first type is intrinsic resistance. Isolates of *E. casseliflavus*/E. flavescens and *E. gallinarum* demonstrate an inherent, low-level resistance to vancomycin. The second type of vancomycin resistance in enterococci is acquired resistance. Enterococci can become resistant to vancomycin by acquisition of genetic information from another organism. Most commonly, this resistance is seen in E. faecium and E. faecalis, but also has been recognized in E. raffinosus, E. avium, E.durans, and several other enterococcal species (4).

They are considered to be pathogens that can cause nosocomial infections, while enterococcal infections have been thought to be endogenous and arising from human's own flora. Frequent use of vancomycin, cephalosporins and aminoglycosides may be related with the increase in nosocomial enterococcal infections (5).

Bacteremia caused by *Enterococcus* is observed more frequently than endocarditis and its frequency is increasing gradually. Nosocomial Enterococcal bacteremia may be polymicrobial and the source is intra-abdominal infections and urinary system in general. The wounds (especially thermal wounds, decubitus ulcers or diabetic foot infections) pelvic sepsis, intravenous or intraarterial catheterization or cholangitis form are other entrances (2).

Case Reports

Case 1

An infectious diseases consultation was requested for a 44-year-old woman due to fever occurring during treatment in nephrology/dialysis department for chronic kidney failure. The patient's leukocyte value was 12.00 uL (neutrophil-75%) and the CRP level was 170. After blood culture was obtained, daptomycin 1x6 mg/kg/once every two days and imipenem 2x250 mg/day were administered to the patient. Blood culture was incubated using a Bact/Alert 3D device (bioMerieux, France). When the blood culture was signalized, it was incubated at 35 ºC for 18-24 hours by planting in EMB, chocolate agar and 5% sheep blood agar. The growth colonies were transferred to catalase test and gram stain. The growth bacteria in the blood culture were identified as *E. casseliflavus*. Bacteria identification and antibiogram tests were performed using conventional techniques as well as Vitek 2 automated system (bioMerieux, France). Antibiotic sensitivity tests were carried out according to the guidelines of the Clinical and Laboratory Standards Institute (6). The isolates were determined to be susceptible to ampicillin, gentamicin 120, streptomycin 300, ciprofloxacin, teicoplanin, tigecycline, and tetracycline and intermediate susceptible to erythromycin, but resistant to clindamycin, vancomycin, linezolid, trimethoprim sulfamethoxazole.

A vancomycin minimum inhibitory concentration (MIC) of 32 µg/ml was determined using E-test (bioMerieux, France). The MIC value for teicoplanin was <0.5 µg/ml. Imipenem treatment was finalized on the third day. Daptomycin treatment was continued and dialysis catheter of the patient was withdrawn. Echocardiography revealed no evidence of endocarditis. Following the resolution of fever, the leukocyte value was 10.000 uL (73% neutrophile) and CRP regressed to 75. The patient was discharged after full recovery.

Case 2

An infectious diseases consultation was requested for a 21-year-old woman due to fever occurring during treatment in nephrology/dialysis department for chronic kidney failure. The patient's leukocyte value was at 12.700 uL (neutrophil-80%) and the CRP level was 135. After blood culture was obtained, daptomycin 1x6 mg/kg/once every two day and cefepime 1x1 g/day were empirically administered. Blood culture was incubated using a Bact/Alert 3D device (bioMerieux, France). When the blood culture was signalized, it was incubated at 35ºC for 18-24 hours by planting in EMB, chocolate agar and 5% sheep blood agar. The growth colonies were transferred to catalase test and gram staining. The growth bacteria in blood culture were identified as *E. casseliflavus*. Bacteria identification and antibiogram tests were performed by using conventional techniques as well as Vitek 2 automated system (bioMerieux, France). The isolates were determined to be susceptible to ampicillin, streptomycin 300, ciprofloxacin, teicoplanin, tigecycline, erythromycin, and tetracycline, on the other hand, resistant to gentamicin 120, clindamycin, vancomycin, linezolid, and trimethoprim/sulfamethoxazole. A vancomycin minimum inhibitory concentration (MIC) of 8 µg/ml was determined using E-test (bioMerieux, France). The MIC value for teicoplanin was <0.5 µg/ml. Cefepime treatment was finalized on the third day. The treatment with daptomycin

was continued, dialysis catheter of the patient was withdrawn. Echocardiography revealed no evidence of endocarditis. After the resolution of fever, the leukocyte value at 8500 uL (neutrophil-70%) and CRP regressed to 45. The patient was discharged after full recovery.

Since the patients were treated in single-bed patient rooms in the nephrology clinic, there was no need to take isolation precautions, but rectal swap specimens were subjected to analysis. Vancomycin-resistant *Enterococcus* (VRE) did not grow in rectal swabs.

Discussion

The Enterococci, which are members of gastrointestinal system flora in human and animal alike, have become important nosocomial pathogens (7,8). When they are detected as a factor in blood cultures, patients should be followed without ignoring their potential for high mortality.

Enterococcus casseliflavus, *E. gallinarum* and E. flavescens, the motil types of *Enterococcus*, have the chromosomally vanC gen with non-transferable characteristic. Thus, they produce low-level intrinsic vancomycin resistance. Also, they are susceptible to teicoplanin (5). In these strains, the value of MIC for vancomycin is generally between 8 and 16 µg/ml (intermediate). This resistance phenotype includes sub-types such as vanC-1, vanC-2 and vanC-3. Moreover, it has been considered that the genes are specific for the types.

Beside with being more frequent, vanC-1 in E. gallinarum, vanC-2 in *E. casseliflavus* and vanC-3 in E. flavescens; *E. casseliflavus* and E. flavescens are likely to represent the same type and vanC-2 and vanC-3 are similar at the ratio of 98% (9).

While Edlund and colleagues observed rapid decrease in the quantity of *Enterococcus* faecium *Enterococcus* faecalis and *Enterococcus* durans during research of the effect of oral vancomycin usage to normal intestinal flora in Sweden; they found out a significant increase in *E. casseliflavus* ve *E. gallinarum* colonization on 21st day (10). It is a significant research which demonstrates the rising risks of capturing serious infections depending on motil *Enterococcus* with intrinsic vancomycin resistance for patients receiving oral vancomycin treatment.

In our patients, prolonged hospital stay due to chronic kidney failure and also being in the hemodialysis unit can be considered as the reason for *E. casseliflavus* bacteremia.

In a survey, blood cultures from which *Enterococcus* species were recovered at the University of Nebraska Medical Center between 1987 and 1996, it was found that there were 486 cases of enterococcal bacteremia identified (11). *E. casseliflavus* was monitored in 5 patients (1%), *E. gallinarum* in 3 (0.6%). One patient had hepatic abscess due to *E. gallinarum* and 9 of 11 blood cultures were positive in this patient. Clinical improvement was achieved in this patient within 48 hours treatment with ampicillin/sulbactam. No primary source for bacteremia was detected in a patient in whom *E. casseliflavus* was recovered from cultures. One patient had peritonitis due to *E. casseliflavus* and all 4 blood cultures yielded positive results. This patient responded to ampicilline and gentamicin treatment after 48 hours with resolution of the fever. All patients with *E. casseliflavus* and *E. gallinarum* bacteremia (8/486) were immunosuppressed and six of them ha received organ transplantation (4 liver transplants, 2 bone marrow transplants).

In a study from Rochester reporting 20 cases of *Enterococcus* gallinarum and *Enterococcus* casseliflavus/ flavescens bacteremia in humans from 1992 through 1998 it was found that 4 cases of bacteremia were due to *E. casseliflavus* and 16 cases of bacteremia were caused by E. gallinarum, 19 patients had underlying conditions including malignancy, receipt of transplant, and Caroli's disease. Polymicrobial bacteremia was present in 9 patients (12).

In a study performed in a 2200-bed tertiary care-affiliated training hospital in Korea, the most comprehensive study published in this field, 56 cases of bacteremia caused by *E. casseliflavus* or *E. gallinarum* diagnosed between the years 1998 and 2003 were retrospectively analyzed (13). Of 13.891 positive blood cultures, *Enterococcus* species were present in 949. *E. casseliflavus* or *E. gallinarum* was isolated from 85 cultures (8.9%). Polymicrobial bacteremia was detected 25 of 56 cases (44.6%) and the most frequently observed organisms were gram-negative bacilli. The median age of the patients (29 males, 27 females) was 59.1 years. In all patients, underlying diseases (biliary disease in 75%, solid cancer in 44.6%) were detected. The presence of biliary drainage catheters was the factor predisposing 21 patients (37.5%) to bacteremia . However, bacteremia due to *E. casseliflavus* and *E. gallinarum* was associated with a low risk of mortality. Also, the patients positively responded to the treatment in our cases.

The emphasis was put on the importance of immunosuppression by Papas and colleagues in their report of a case of polymicrobial bacteremia including *E. casseliflavus*, Escherichia coli and Morganella morganii developed soon after a liver biopsy in an 80-year-old woman (14).

In their retrospective study, Koganemaru et al. investigated the clinical and microbiological characteristics of bacteremia caused by intrinsically vancomycin-resistant enterococci in a university hospital in Japan. *E. casseliflavus* was identified in 4 cases and *E. gallinarum* in 5 cases. Among 9 cases of bacteremia caused by vanC-type, 5 cases were neutropenic and and 4 cases had biliary tract infection (15). In that period, vanC-type enterococci were responsible from 12% of all Enterococcal bacteremia. This situation was interpreted as vanC-type enterococci cause bacteremia in Japan more commonly than in areas which has been previously reported.

There is a research related to the fact that E. gallinarum, another motil *Enterococcus* that is hardly isolated as a factor of bacteremia, has performed high level resistance of vancomycin (MIC=64 µg/ml) and teicoplanin (MIC=32 µg/ml) (16). In this case reported from Argentina, it was detected that both vanC1 and vanA gens were found in the enterococcal genoma. A similar resistant type was encountered in a 3-month survey performed in 2009, in Brazil to investigate the presence of faecal carriage of vancomycin resistant enterococci (17). When pulsed-field gel electrophoresis (PFGE) was applied to 7 isolates, in which a high level of glycopeptide resistance (vancomycin MIC>256 and teicoplanin MIC=64-96 µg/mL) was detected, it was observed that vanA and vanC1 genes co-existed extraordinarily. It was emphasized that it might have an importance in nosocomial infections as a special pattern of resistance.

In a case of *E. casseliflavus* bacteremia reported from our country, *E. casseliflavus* carriage was detected in rectal swab samples in 6 of 10 patients who were treated in the intensive care unit (18). This was the case of a patient developing acute renal failure, receiving hemodialysis and was cured with linezolid following growth in the blood culture obtained in the intensive care unit and the patient was discharged with full recovery after 50 days.

In another study, Arca and colleagues detected the development of bacteremia with *E. gallinarum* (in 1 case of 67 blood cultures) and *E. casseliflavus* (in 1 case of 67 blood cultures). Both of these cases had received treatment in the gastroenterology clinic (19).

In a research on the antibiotic resistance of *Enterococcus* species, Berktaş and colleagues found that 3 of 113 isolated *Enterococcus* strains were *E. casseliflavus*/*E. gallinarum* (20).

As a result, apart from the lack of enough frequency of encountering as a factor in blood cultures, this has to be kept in mind that *E. casseliflavus* should not be ignored in patients with biliary tract diseases and immune-deficiency, in particular.

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