Case Report

Joon Rok Nam, M.D.¹
Myoung Soo Kim, M.D.¹
Chae Heuck Lee, M.D.¹
Dong Hee Whang, M.D.²

Departments of Neurosurgery¹
and Laboratory Medicine²
Seoul Paik Hospital
Inje University
College of Medicine, Seoul
Korea

Linezolid Treatment for Osteomyelitis due to *Staphylococcus Epidermidis* with Reduced Vancomycin Susceptibility

Limited therapeutic options are available for vancomycin intermediate-resistant *Staphylococcus epidermidis* (VISE) infections and no optimum therapy has been established. We report a case of VISE skull osteomyelitis that was successfully treated with linezolid. The patient was a 53-year-old man who presented with headache, nausea and dysphasia. Brain computerized tomography (CT) demonstrated a subdural hematoma in the left hemisphere. Craniotomy and hematoma evacuation was performed and he showed good recovery despite a scalp wound infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The organism isolated from the scalp wound was sensitive to vancomycin. The patient was treated with intravenous vancomycin for 44 days. However, he showed a high fever, persistent positive methicillin-resistant *Staphylococcus epidermidis* (MRSE) blood cultures, and a deteriorating clinical status. He underwent infected skull bone flap removal and linezolid treatment for 35 days. During one year of follow up, he has not had any further episodes of osteomyelitis or fever. Linezolid has shown to be effective agent to eradicate osteomyelitis caused by VISE.

KEY WORDS : Vancomycin-resistance · *Staphylococcus epidermidis* · Linezolid · Skull osteomyelitis.

INTRODUCTION

Coagulase-negative *Staphylococci* have emerged over the past decade as major pathogens. Previously considered contaminants, these organisms are the most common cause of prosthetic-device-related infection. As methicillin resistance is particularly common among coagulase-negative *Staphylococci*, vancomycin remains the major antibiotic used to treat these infections. In vitro, resistance to vancomycin among *Staphylococci* is extremely uncommon. However, *Staphylococcal* infections due to foreign body frequently do not respond to vancomycin, and removal of the prosthetic device is often required⁴⁾.

Linezolid, a member of a novel class of drugs, the oxazolidinones, has excellent in vitro activity against a broad range of common gram-positive organisms, including coagulase-negative *Staphylococci*, and achieves excellent cerebrospinal fluid penetration¹⁾. Here, we describe a patient with skull osteomyelitis caused by *Staphylococcus epidermidis* with reduced vancomycin susceptibility who was successfully treated with linezolid.

CASE REPORT

The patient was a 53-year-old man who presented with headache, nausea and dysphasia. His medical history was significant for valvular heart disease. He had undergone aortic valve replacement 18 years and mitral valve replacement four years before presentation. In addition, pacemaker implantation was performed one year before presentation. He had been taking warfarin for 18 years. Neurological examination showed no abnormality except for mild dysphasia. Brain computerized tomography (CT) demonstrated a subdural hematoma in the left hemisphere (Fig. 1). Craniotomy and hematoma evacuation were

Fig. 1. Computerized tomography at admission shows subdural hematoma in left cerebral hemisphere.

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• Address for reprints :
Myoung Soo Kim, M.D.
Department of Neurosurgery
Seoul Paik Hospital
Inje University
College of Medicine
85 Jeo-dong 2-ga, Jung-gu
Seoul 100-032, Korea
Tel : +82-2-2270-0032
Fax : +82-2-2270-0573
E-mail : hanibalkms@hanmail.net

Fig. 2. Computerized tomography after first operation shows removed subdural hematoma and newly developed intracerebral hematoma in left temporal lobe.

Fig. 3. Simple skull X-rays taken 20 days (A) and 66 days after first craniotomy (B) showing the progression of an osteolytic lesion in upper portion of bone flap and in the adjacent surrounding bone.

Fig. 4. Minimal inhibitory concentration of vancomycin for *Staphylococcus epidermidis* isolated from blood culture demonstrates initial susceptible (2-4 mg/L) and later intermediate-resistant (8 mg/L). x-axis : date, y-axis : Minimal inhibitory concentration of vancomycin, mg/L, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of infected bone flap removal.

performed. He made a recovery despite a postoperative intracerebral hemorrhage in the temporal lobe (Fig. 2). However, scalp wound infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) was developed on 12 days after the first operation. The organism isolated from the scalp wound was sensitive to vancomycin (minimal inhibitory concentration, 2 mg/L). Therefore, the patient was treated with intravenous vancomycin since 22 days after the first operation. The scalp wound infection was improved at 3 weeks after use of intravenous vancomycin. He showed good clinical status except for mild dysphasia, and had no fever. However, he showed persistent positive methicillin-resistant *Staphylococcus epidermidis* (MRSE) blood cultures. We speculated that this organism was originated from endocarditis. Therefore, we continued the intravenous vancomycin for 44 days. Nevertheless, he showed a persistent high fever and mild fatigue. A plain skull X-ray taken 66 days after the first craniotomy demonstrated an osteolytic lesion suggesting osteomyelitis (Fig. 3). He underwent infected bone flap removal and received intravenous teicoplanin for 7 days. Despite of the second operation and intravenous teicoplanin treatment, he became drowsy with sepsis on 7th day after the second operation. Laboratory finding in serum revealed Anti-thrombin III 102.2%, D-dimer 0.42 ug/ml, FDP 64.0 ug/ml and fibrinogen 569 mg/dl on 9th day after second operation. Susceptibility test of *Staphylococcus epidermidis* for vancomycin using automated methods (Vitek II, version 4.02 software, Biomerieux, Hazelwood, Missouri) after the clinical deterioration showed intermediate-resistance (minimal inhibitory concentration: 8 mg/L ; Fig. 4). We tried oral linezolid treatment. And, the sepsis was improved (Figs. 5, 6, 7). We continued linezolid treatment for 35 days.

During one year after discharge, he has not had any episodes of osteomyelitis nor fever.

DISCUSSION

Coagulase-negative *Staphylococci* are normal commensals of the skin, anterior nares, and ear canals of humans. In the past, these organisms were regarded as nonpathogenic and were rarely reported to cause serious infection⁵. With the emergence and spread of coagulase-negative *Staphylococci* strains displaying resistance to semisynthetic penicillins, vancomycin became the first-line agent for the

management of infections caused by these microorganisms. However, widespread use of vancomycin has recently led to the emergence of coagulase-negative *Staphylococci* isolates with decreased susceptibility to vancomycin, primarily in *Staphylococcus haemolyticus* and, to a lesser extent, *Staphylococcus epidermidis* strains^{10,12}. In vitro resistance to vancomycin among *Staphylococci* is extremely uncommon¹⁰; however, foreign body infections of these organisms frequently do not respond to vancomycin, and removal of the prosthetic devices is often required².

Glycopeptide resistance among the *Staphylococci* appears to be a function of heteroresistant subpopulations¹³ and antibiotic selection in vivo⁹. Dunne et al³. reported the potential for *Staphylococci* with reduced susceptibility to vancomycin to be overlooked in the clinical laboratory. The decreased susceptibility of coagulase-negative *Staphylococci* to glycopeptide antibiotics appears to be a function of heterogeneous subpopulations of resistant organisms that occur at variable frequencies⁹. Theoretically, as in this patient, the vancomycin intermediate-resistant *Staphylococcus epidermidis* isolated from the blood cultures might have been induced from heteroresistant subpopulations because of long-term use of vancomycin.

MRSA and coagulase-negative *Staphylococci* is frequently seen in nosocomially related osteomyelitis. Vancomycin-resistant *Enterococcus* (VRE) *faecium*, a nosocomial isolate, is another gram-positive coccus that can produce bone infections and, like methicillin-resistant *Staphylococci*, is susceptible to only a limited number of antibiotics⁸. Patients allergic or intolerant to, or failing, vancomycin, or unable to tolerate long-term intravenous therapy, have been left with

Fig. 5. C-reactive protein during antibiotics treatment. x-axis : date, y-axis : C-reactive protein, mg/dL, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected bone flap removal.

Fig. 6. Erythrocyte sedimentation rate during antibiotics treatment. x-axis : date, y-axis : erythrocyte sedimentation rate, mm/hr, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected bone flap removal.

Fig. 7. White blood cell count in peripheral blood during antibiotics treatment. x-axis : date, y-axis : white blood cell count , $\times 10^3/\mu\text{L}$, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected bone flap removal.

few or no therapeutic options. Thus, newer agents (including quinupristin/dalfopristin and linezolid) may be required for the optimal treatment of osteomyelitis caused by these organisms. Linezolid, however, is the only agent approved for treating MRSA infections and has activity against both VRE *faecium* and VRE *faecalis*⁶⁾. The attractive features of linezolid are the 100% orally bioavailable dosage forms and adequate bone penetration⁷⁾. Duration-related adverse effects, including reduction in platelets and hemoglobin, are expected. Hematological indices decrease slowly over time, and can be detected with the appropriate monitoring of complete blood cell counts during treatment with linezolid, and are reversible upon cessation of linezolid⁸⁾.

Our case report has several limitations. Only one sensitivity result showed a reduced susceptibility for vancomycin (minimal inhibitory concentration, 8 mg/L). The detection of glycopeptide-resistant coagulase-negative *Staphylococci* in the diagnostic laboratory may be problematic because susceptibility tests, particularly for teicoplanin, which can be influenced by a variety of technical factors, including the basal medium, the addition of supplements like blood or serum, the inoculum size, the incubation time, and the disk contents¹⁴⁾. *Staphylococci* with reduced susceptibility to glycopeptides appear to be best detected in the laboratory by nonautomated quantitative methods (broth and agar dilution tests, E test) using a full 24 hour incubation¹¹⁾. Commercial agar screen plates containing 6 mg/L vancomycin may also be able to detect these isolates, whereas with automated methods the results may differ considerably from one system to another¹¹⁾. However, in this case, continued positive blood cultures, reduced susceptibility to vancomycin and clinical deterioration despite prolonged vancomycin treatment confirmed the development of infection with *Staphylococcus epidermidis* with reduced susceptibility to vancomycin.

CONCLUSION

In summary, patient with osteomyelitis due to vancomycin intermediate-resistant *Staphylococcus epidermidis*

(VISE) who fail to respond to vancomycin can be successfully treated with linezolid.

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