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Case Report

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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 eradiate 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 required[4].

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 penetration[1]. 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

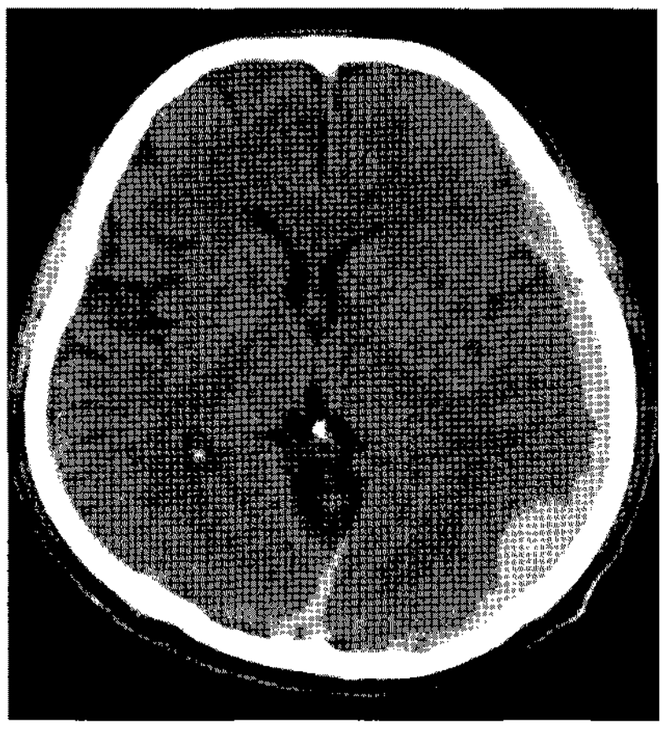

Fig. 1. Computerized tomography at admission shows subdural hematoma in left cerebral hemisphere.

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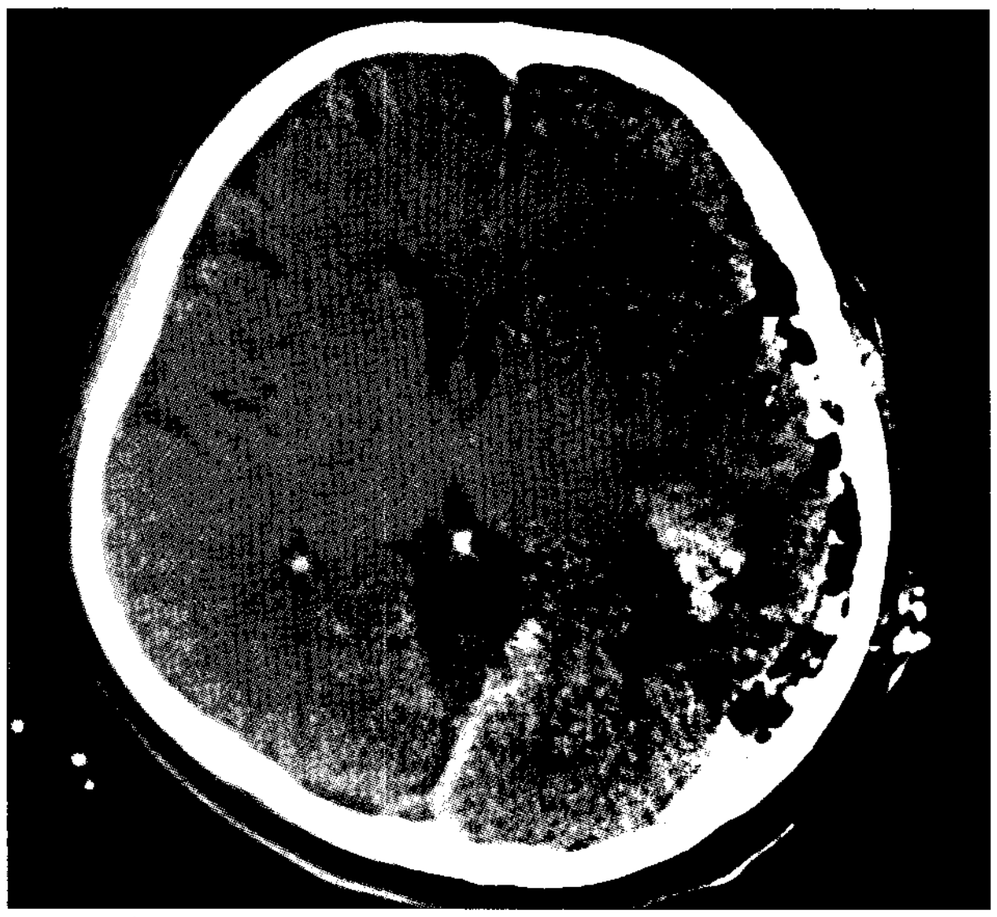

Fig. 2. Computerized tomography after first operation shows removed subdural hematoma and newly developed intracerebral hematoma in left temporal lobe.

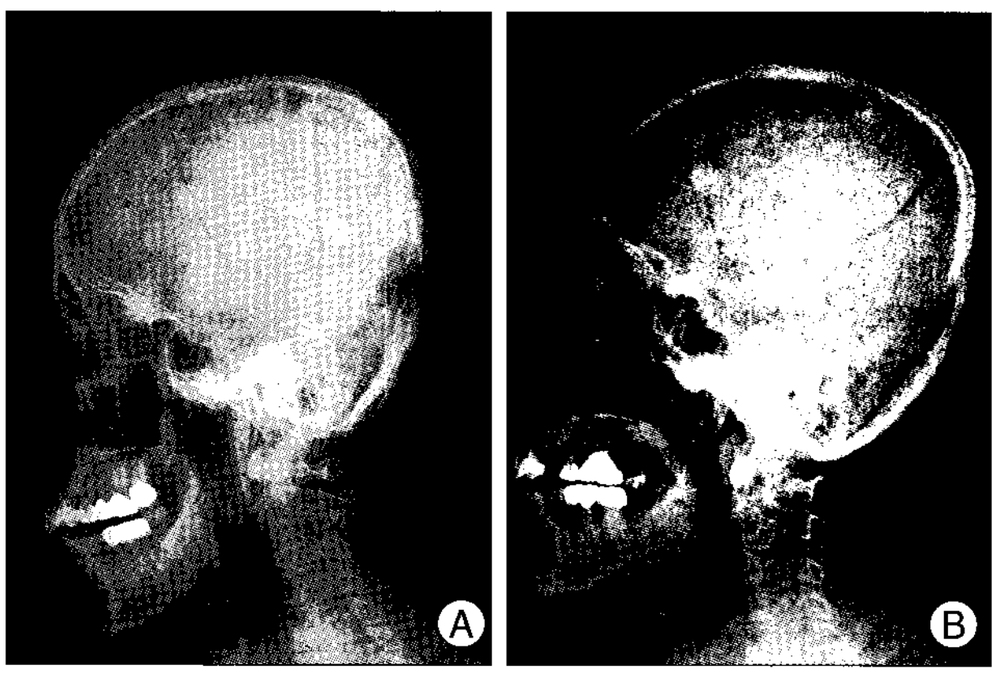

Fig. 3. Simple skull X-rays taken 20 days (A) and 66 days after first craniotomy (B) showing the progression of an osteolytic lesion in upper portion of bone flap and in the adjacent surrounding bone.

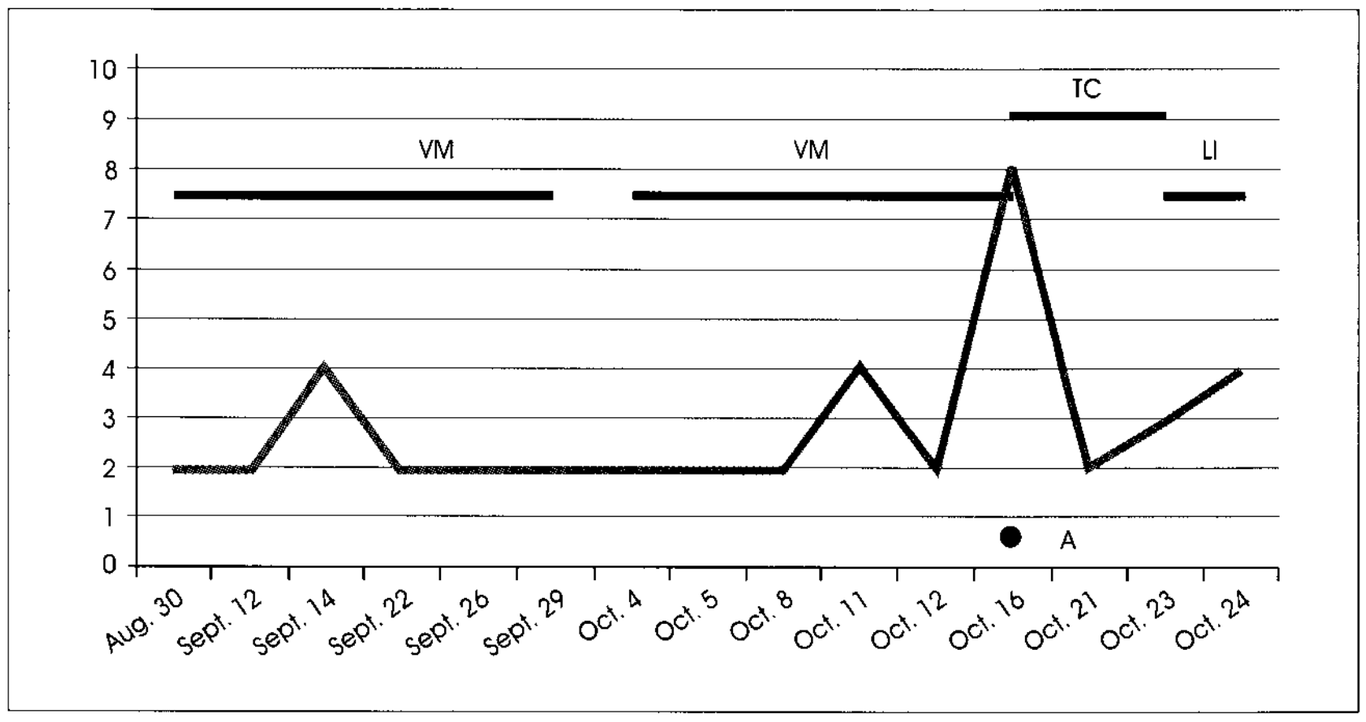

Fig. 4. Minimal inhibitory concentration of vancomycin for *Staphyloccus epidermidis* isolated from blood culture demonstrates initial susceptive (2-4 mg/L) and later intermediate-resistant (8 mg/L). x-axis : date, y-axis : Minimal inhibitory concentration of vancomycin, mg/L, VM : period of vancomycin 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 infection[5]. 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 uncommon[10]; however, foreign body infections of these organisms frequently do not respond to vancomycin, and removal of the prosthetic devices is often required[2].

Glycopeptide resistance among the *Staphylococci* appears to be a function of heteroresistant subpopulations[13] and antibiotic selection in vivo[9]. Dunne et al[3]. 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 frequencies[9]. 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 antibiotics[8]. Patients allergic or intolerant to, or failing, vancomycin, or unable to tolerate long-term intravenous therapy, have been left with

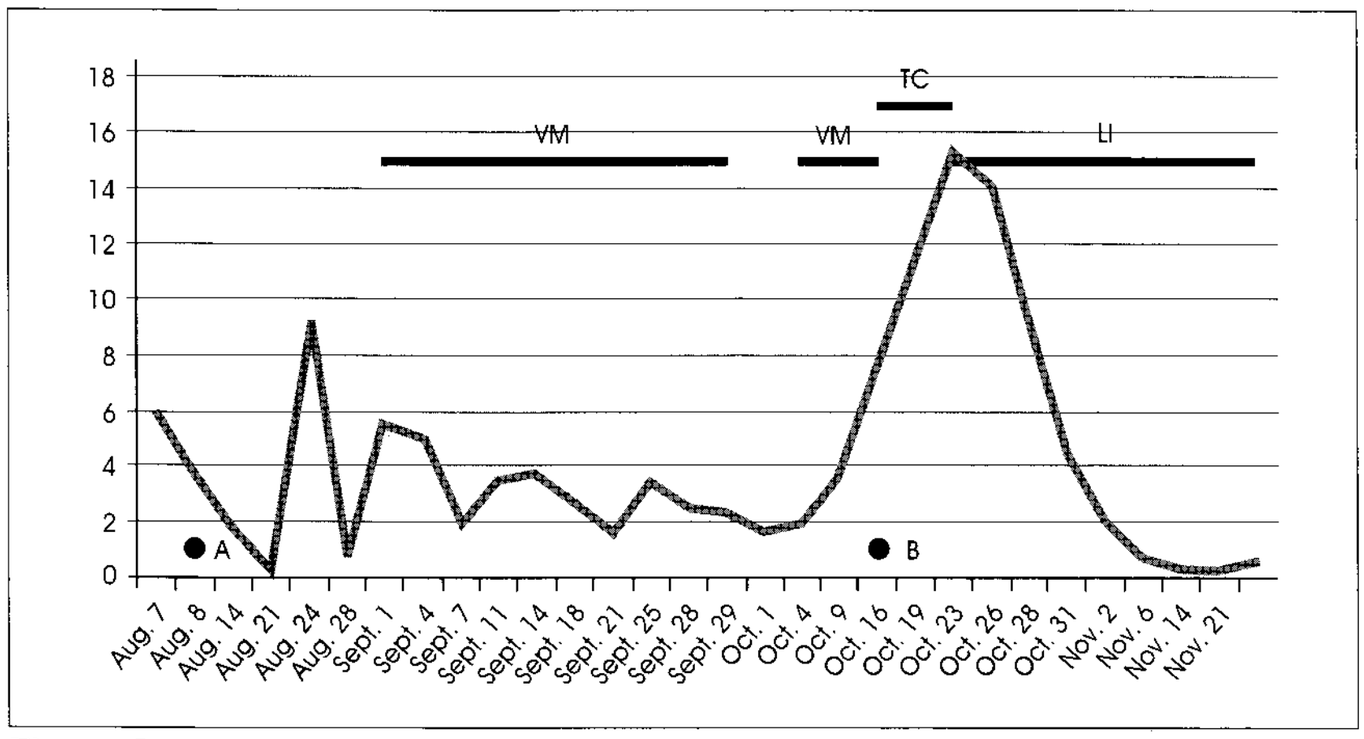

Fig. 5. C-reactive protein during antibiotics treatment. x-axis : date, y-axis : C-reactive protein, mg/dL, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected bone flap removal.

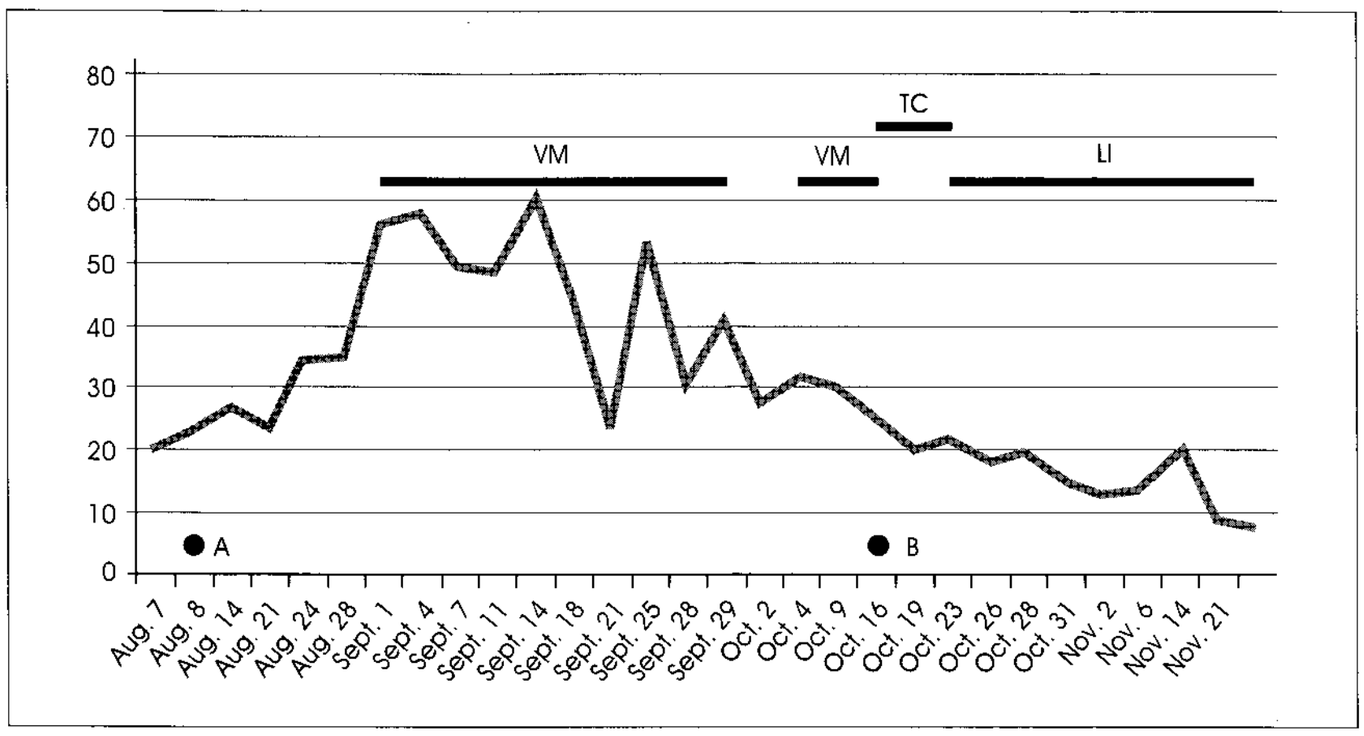

Fig. 6. Erythrocyte sedimentation rate during antibiotics treatment. x-axis : date, y-axis : erythrocyte sedimentation rate, mm/hr, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected bone flap removal.

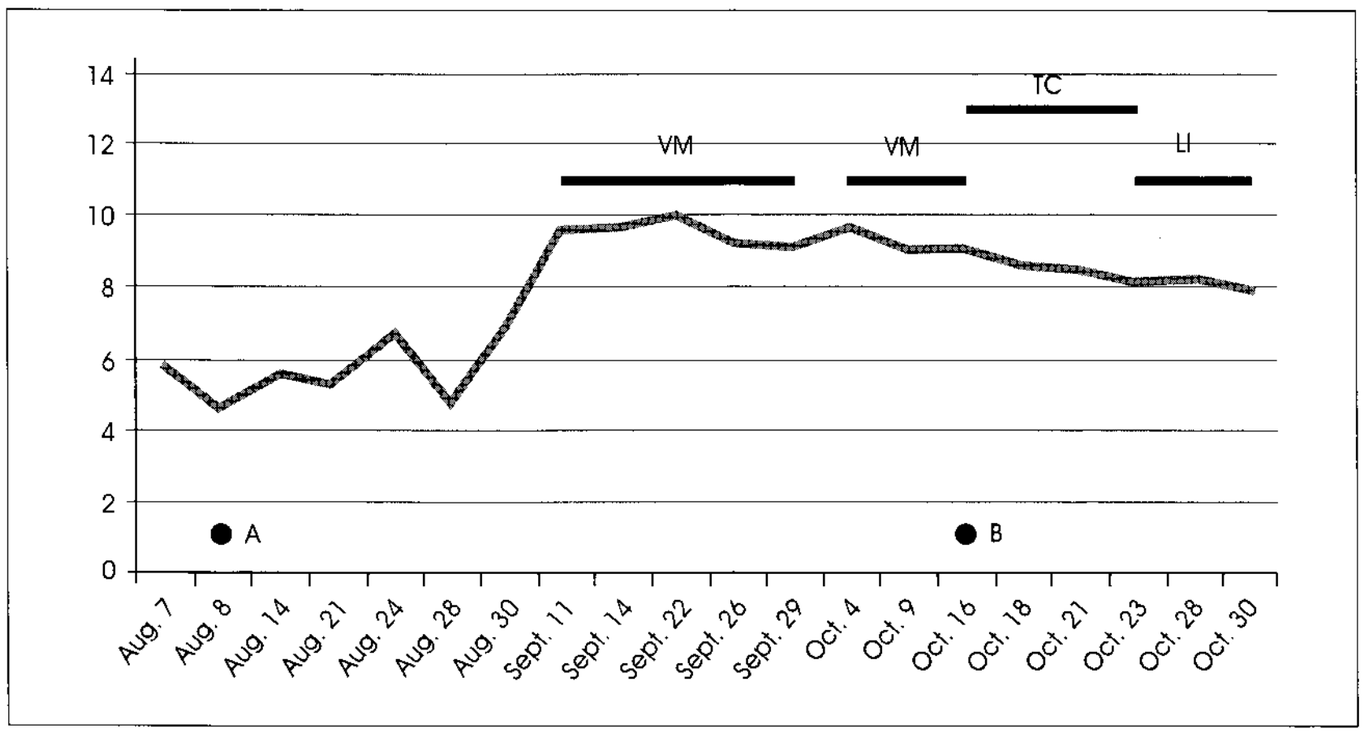

Fig. 7. White blood cell count in peripheral blood during antibiotics treatment. x-axis : date, y-axis : white blood cell count , $\times 10^3/\mu\ell$, VM : period of vancomycin usage, TC : period of teicoplanin usage, LI : period of linezolid usage, A : date of hematoma removal, B : date of infected 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 penetration[7]. 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 linezolid[8].

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 contents[14]. *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 incubation[11]. Commercial agar screen plates containing 6 mg/L vancomycin may also able to detect these isolates, whereas with automated methods the results may differ considerably from one system to another[11]. 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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References

1. Bodogan B, Appelbaum PC : Oxazolidinones : activitiy, mode of action, and mechanism of resistance. **Int J Antimicrob Agents 23** : 113-119, 2004
2. Davenport DS, Massanari RM, Pfaller MA, Bale MJ, Streed SA, Hierholzer WJ Jr : Usefulness of a test for slime production as a marker for clinically significant infections with coagulase-negative staphylococci. **J Infect Dis 153** : 332-339, 1986
3. Dunne WM Jr, Qureshi H, Pervez H, Nafziger DA : Staphylococcus epidermidis with intermediate resistance to vancomycin : elusive phenotype or laboratory artifact? **Clin Infect Dis 33** : 135-137, 2001
4. Farber BF, Kaplan MH, Cloqston AG : Staphylococcus epidermidis extracted slime inhibits the antimicrobial action of glycopeptide antibiotics. **J Infect Dis 161** : 37-40, 1990
5. Garrett DO, Jochimsen E, Murfitt K, Hill B, McAllister S, Nelson P, et al : The emergence of decreased susceptibility to vancomycin in Staphylococcus epidermidis. **Infect Control Hosp Epidemiol 20** : 167-170, 1999
6. Kaatz GW, Seo SM : In vitro activities of oxazolidinone compounds U100592 and U100766 against Staphylococcus aureus and Staphylococcus epidermidis. **Antimicrob Agents Chemother 40** : 799-801, 1996
7. Rana B, Butcher I, Grigoris P, Murnaghan C, Seaton RA, Tobin CM : Linezolid penetration into osteo-articular tissues. **J Antimicrob Chemother 50** : 747-750, 2002
8. Rayner CR, Baddour LM, Birmingham MC, Norden C, Meagher AK, Schentag JJ : Linezolid in the treatment of osteomyelitis : results of compassionate use experience. **Infection 32** : 8-14, 2004
9. Schwalbe RS, Ritz WJ, Verma PR, Barranco EA, Gilligan PH : Selection for vancomycin resistance in clinical isolates of Staphylococcus haemolyticus. **J Infect Dis 161** : 45-51, 1990
10. Schwalbe RS, Stapleton JT, Gilliqan PH : Emergence of vancomycin resistance in coagulase-negative staphylococci. **N Engl J Med 316** : 927-931, 1987
11. Tenover FC, Lancaster MV, Hill BC, Steward CD, Stocker SA, Hancock GA, et al : Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. **J Clin Microbiol 36** : 1020-1027, 1988
12. Veach LA, Pfaller MA, Barrett M, Koontz FP, Wenzel RP : Vancomycin resistance in Staphylococcus haemolyticus causing colonization and bloodstream infection. **J Clin Microbiol 28** : 2064-2068, 1990
13. Wong SS, Ho PL, Woo PC, Yuen KY : Bacteremia caused by staphylococci with inducible vancomycin heteroresistance. **Clin Infect Dis 29** : 760-767, 1999
14. Woodford N, Johnson AP, George RC : Detection of glycopeptide resistance in clinical isolates of gram-positive bacteria. **J Antimicrob Chemother 28** : 483-486, 1991