

CASE REPORT

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Treatment of Meningitis Caused by Vancomycin-Resistant Enterococcus with Synercid

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Vancomycin-resistant enterococci(VRE) are rare cause of meningitis, occurring in immunocompromised patients, severely ill, hospitalized patient, and patients who have undergone neurosurgical procedures. Resistance to vancomycin has increased in frequency during the past few years. Limited therapeutic options are available for VRE infections and the optimum therapy has not been established. We report a case of VRE meningitis that was successfully treated with administration of quinupristin-dalfopristin (Synercid) by both intravenous and intraventricular routes. A brief review of the literature is provided, which indicates that optimal management with Synercid should include daily intraventricular doses of at least 2mg and intravenous 0.5mg/kg every 8 hours. We also review the previously reported cases of VRE meningitis.

KEY WORDS : Vancomycin-resistant enterococcus · Ventriculitis · Quinupristin-dalfopristin.

Introduction

The frequency of *Enterococcus faecium* infections resistant to both ampicillin and vancomycin has increased in recent years⁵. Vancomycin-resistant *Enterococcus faecium* (VREF) has emerged as an important and difficult nosocomial pathogens⁶ to treat. Enterococci are normal flora in the gastrointestinal tract but can cause urinary tract infections, endocarditis, bacteremia; pelvic, intraabdominal and wound infections; and less commonly bone, joint and central nervous

system(CNS) infections^{6,13}. VREF infections occur in severely immunocompromised patients, who are neutropenic or have an underlying malignancies¹⁰.

Anatomical defects of the CNS, prior neurosurgery, and head trauma are the main causes of enterococcal meningitis¹². Common species of enterococci isolated from clinical specimens are *Enterococcus faecalis* (80~90%), *Enterococcus faecium* (5~20%), and other species including *Enterococcus gallinarum*¹².

There are few therapeutic options for the treatment of VREF infections. We describe the successful treatment of VREF ventriculitis with quinupristin-dalfopristin.

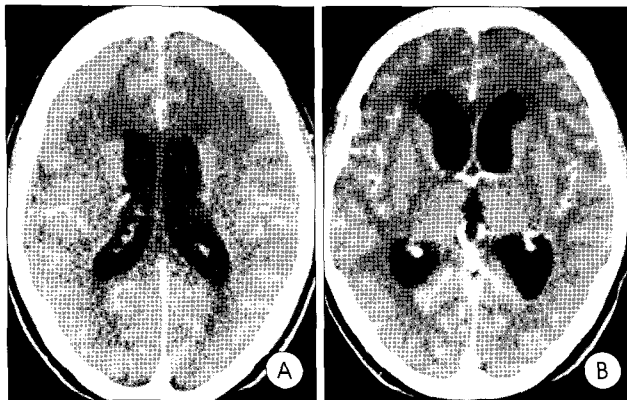


Fig. 1. Contrast-enhancement computed tomography showing hydrocephalus and enhancement along the ventricular wall indicating ventriculitis(A, B).

Case Report

A 48-year-old female patient presented with 3-year history of both foot drops and voiding difficulty. Tethered cord with lumbosacral lipoma was diagnosed on magnetic resonance image(MRI) scan. The lipoma was removed and the cord was untethered with sectioning of filum terminale. On postoperative 4 days, cerebrospinal fluid(CSF) collection in operative wound was identified, and it was drained out. On postoperative 1 month, the patient revealed headache, neck stiffness and disorientation, accompanying with intermittent high fever. The analysis of CSF revealed the following values; WBC

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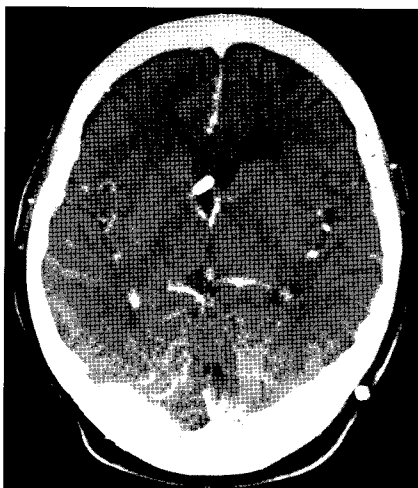


Fig. 2. Contrast-enhancement computed tomography showing restoration of ventricle enlargement and no ependymal enhancement.

1,800 cells/mm³ (98% segmented neutrophils and 2% lymphocytes), glucose 10mg/dl and protein 195mg/dl. Under the impression of meningitis, empirical antibiotic therapy, including cefotaxime and vancomycin were given for 48 days. However, she showed no clinical improvement. The culture of the CSF yielded VREF resistant to ampicillin, vancomycin, levofloxacin and sensitive to tetracycline and quinupristin-dalfopristin. Her brain computerized tomography (CT) scan showed hydrocephalus and ependymal enhancement indicating ventriculitis (Fig. 1), and extraventricular drainage (EVD) was performed. The patient was given intravenous and intraventricular quinupristin-dalfopristin of 7.5mg/kg every 8 hour and 1mg once a day, respectively. The intraventricular dose was gradually increased to 4mg per day until CSF culture showed negative conversion. At one month after treatment, her CSF turned to be sterile over 3 times. The last analysis of CSF revealed WBC 24 cells/mm³ (100% lymphocytes), glucose 57mg/dl and protein 41.0mg/dl. She recovered uneventfully. At two months after treatment, ventriculoperitoneal shunt was performed for hydrocephalus and brain CT scan showed restoration of ventricle enlargement and no ependymal enhancement (Fig. 2). She was followed up for 6 months after shunt operation and there was no evidence of recurrent infection.

Discussion

Enterococcal meningitis tends to occur in patients with chronic medical conditions that are often associated with the use of immunosuppressive therapy, underlying CNS diseases (trauma, surgery, and epidural catheter), gastrointestinal pathology, and strongyloides species^{11,13}. The typical presentation of enterococcal meningitis is rapid onset of fever, signs of meningeal irritation, and altered sensorium, sometimes a subacute presentation has also been described^{2,11}. CSF findings are usually consistent with infection demonstrated by pleocytosis with neutrophil predominance, elevated protein levels, and hypoglycorrhachia^{11,13}. The mortality rate of patients with

enterococcal meningitis is high, ranging from 13% to 33%^{1,11,13}.

There were several reports^{6,8,10,13} of successful treatment of CNS infections caused by VREF with intraventricular and intravenous quinupristin-dalfopristin; intrathecal teicoplanin combined with intravenous clindamycin, rifampin and ampicillin; and intravenous chloramphenicol⁶. However, optimal therapy for VRE and VREF meningitis has not been established.

It is possible to treat ventriculitis with intravenous antibiotics administration in early stage. If there were no responses with intravenous antibiotics therapy, antibiotics could be administered directly into the ventricles through spinal tapping or EVD catheter⁷. The cessation of intraventricular antibiotics is usually recommended as disappearance of inflammation on CSF findings; improvement of clinical symptoms, including fever; negative finding of CSF cultures over three times⁷.

Quinupristin-dalfopristin (Synercid; Aventis Pharma, Inc., Parsippany, NJ) is a combination of two intravenous streptogramin antibiotics formulated in a 30 : 70 ratio^{5,8}. Although the individual component is primarily bacteriostatic, the combination is often bactericidal, more potent, and may be active even when there is resistance to each component⁴. The synergistic activity of the compound is ascribed to conformational change in the bacterial ribosome after dalfopristin binding^{3,4}. Quinupristin-dalfopristin displays activity against gram-positive organisms such as *Enterococcus faecium* isolated that are resistant to vancomycin and ampicillin⁵. Quinupristin-dalfopristin is bacteriostatic against the great majority of VREF strains but in vitro data show bactericidal potential against staphylococci that are not constitutively MLSB resistant⁴.

The criteria of the National Committee for Clinical Laboratory Standards for susceptibility, intermediate susceptibility, and resistance to quinupristin-dalfopristin are ≤ 1 , 2, and $\geq 4 \mu\text{g/ml}$, respectively^{4,9}. The recommended dosage is 7.5 mg/kg given every 8 hour, and patients actually receive an average of 20mg/kg per day⁴. It must be given intravenously, generally by deep catheter to avoid venous irritation⁴. The patient in this report was given to intravenous injection via a subclavian line. Intrathecal dosing was recommended to 1 or 2mg/day for 5~33 days⁹. Intravenous and intraventricular injections were given to this patient for 42 days. CSF concentrations of quinupristin with its active metabolites and dalfopristin with its active metabolite were greater than the MIC of the VREF (MIC $< 0.5 \mu\text{g/ml}$) for almost 4 hours after the 1mg dose and for at least 8 hours after the 2mg dose⁹. Quinupristin-dalfopristin affects clearance of medications via the cytochrome P450 system, with the potential for major drug interactions⁴. A variable number of patients would experience myalgias and/or arthralgias that can be severe enough to require dose reduction or administration of opiate analgesics⁴. The patient in this report didn't show

any evidence of drug-induced side reaction.

The literature contains no report about successful treatment with Synercid in the patient with a ventriculitis in Korea.

Conclusion

Enterococci rarely cause CNS infections. Intrathecal dosing of quinupristin-dalfopristin with intravenous administration was effective in our patient against a ventriculitis caused by VREF infection. We obtained a good result of VREF ventriculitis treated with quinupristin-dalfopristin.

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