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CASE REPORT

Vertebral osteomyelitis caused by vancomycin-tolerant methicillin-resistant *Staphylococcus aureus* bacteremia: Experience with teicoplanin plus fosfomycin combination therapy

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An 85-year-old female presented with fever and consciousness disturbance for 3 days. The patient's blood culture subsequently revealed persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia despite the administration of vancomycin or teicoplanin monotherapy. Gallium inflammation scan and magnetic resonance image of the spine disclosed osteomyelitis and discitis at the level of L4—5. Surgical debridement was not feasible in this debilitated patient. Because of the creeping minimal inhibitory concentration of vancomycin of the causative isolate (1.5 μg/mL) and clinical failure with glycopeptide monotherapy, we changed the antibiotic therapy to a fosfomycin and teicoplanin combination therapy. The patient showed improved clinical response in terms of her enhanced consciousness as well as subsidence of persisted bacteremia. Despite the potential side effects of fosfomycin (such as diarrhea and

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hypernatremia), it combined with a glycopeptide may be an alternative therapy for invasive refractory MRSA infections.

Introduction

Staphylococcus aureus is the most common causative agent of hematogenous vertebral osteomyelitis among adults, accounting for over 60% of cases.[1] Emergence of the methicillin-resistant *S. aureus* (MRSA) strain has further complicated management of patients with vertebral osteomyelitis. The increasing minimal inhibitory concentration (MIC) of MRSA now accounts for a large proportion of invasive *S. aureus* infections.[2] MRSA-related infections often result in higher mortality rates and longer duration of hospitalization.[3,4] The Clinical and Laboratory Standards Institute lowered the susceptibility breakpoint of *S. aureus* from 4 μg/mL to 2 μg/mL, teicoplanin 8 μg/mL and fosfomycin 64 μg/mL.[5] Vancomycin or teicoplanin has been the antibiotic of choice for MRSA bacteremia. However, many alternative agents and combination therapies are considered as the salvage therapy of MRSA bacteremia when vancomycin treatment fails.[6,7]

Fosfomycin is a phosphoenolpyruvate analog produced by *Streptomyces* that inhibits enolpyruvate transferase, which prevents the formation of the peptidoglycan cell wall.[8] *In vitro* studies have confirmed the effectiveness of fosfomycin in combination with other antistaphylococcal agents, including vancomycin and teicoplanin, when conventional glycopeptide therapy fails.[9] Moreover, high concentrations of fosfomycin in bone tissue have been proved to be effective for treating osteomyelitis.[10]

We describe a case of lumbar osteomyelitis and discitis with persistent MRSA bacteremia refractory to vancomycin treatment. The patient was treated successfully with a combination therapy of fosfomycin and teicoplanin.

Case report

An 85-year-old female had a history of type 2 diabetes mellitus and was bedridden following a cerebral vascular accident. She had recurrent multiple pressure sores over lumbosacral areas. On admission, she was presented with fever and disturbed consciousness for 2 days. Physical examination revealed blood pressure of 89/68 mmHg and heart rate of 98 beats per minute. She had moderate respiratory distress, with a respiratory rate of 22 breaths per minute, and a body temperature of 39.5°C. The patient had multiple pressure sores over the lumbosacral and bilateral ankles area. Her white blood cell count was 26,960/μL, with 85% neutrophils and 9% band forms; platelet count 125,000/μL; and hemoglobin concentration 11.5 g/dL. The patient's biochemistry data were as follows: blood urea nitrogen 26 mg/dL, creatinine 1.26 mg/dL, randomized glucose 186 mg/dL, sodium 143 mmol/L, and potassium 3.3 mmol/L. Serum level of C-reactive protein (CRP) was 19.31 mg/dL. Urinalysis showed pyuria and bacteriuria. Her chest X-ray showed no evidence of active lung infection. Brain computed tomography revealed no intracerebral hemorrhage or evidence of newly onset cerebral infarction. Abdominal sonography revealed no biliary tract lesion. The empirical antibiotic of cefoperazone/sulbactam (2/1 g) was administered intravenously (i.v.) every 12 hours.

On the 4th admission day, urine culture yielded *Escherichia coli* and blood culture revealed MRSA. The antibiotic treatment was changed to ertapenem 1 g i.v. every 24 hours and vancomycin 1 g i.v. drip for 1 hour every 12 hours to cover both agents based on our laboratory susceptibility test (vancomycin MIC: 1.0 μg/mL by E test). One week later, blood cultures yielded MRSA (vancomycin MIC: 1.5 μg/mL by E test) repeatedly. Her urinalysis showed no pyuria in repeated tests and urine culture was negative. Echocardiography disclosed no evidence of infective endocarditis. Vancomycin was changed to teicoplanin (MIC: 1.0 μg/mL by E test) 400 mg once a day i.v. due to renal function deterioration and persisted bacteremia. MRSA bacteremia persisted despite a 2-week course of intravenous teicoplanin therapy. Erythrocyte sedimentation rate (ESR) was 91 mm/h and CRP was 11.7 mg/dL.

Magnetic resonance imaging of the L-spine indicated osteomyelitis and discitis at L4 and L5, with the involvement of bilateral psoas muscles and epidural abscess with low signal intensity on T1-weighted image and low-to-isointense signal on T2-weighted images, enhancement after gadolinium injection (Fig. 1A) and transverse view (Fig. 1B). Surgical debridement was not performed on the patient due to her poor performance status as well as the refusal of the patient's family. The antibiotic regimen was changed to a combination therapy comprising fosfomycin 4 g i.v. every 6 hours and teicoplanin 400 mg once daily. After commencing this combination regimen, blood cultures became sterile 1 week later.

The patient received a 5-week course of fosfomycin plus teicoplanin combination therapy. Serum ESR and CRP decreased to 35 mm/h and 2.1 mg/dL, respectively. The patient was discharged and in our outpatient clinic received a combination therapy comprising intramuscular injections of teicoplanin 400 mg twice a week, oral fusidic acid 500 mg every 8 hours, and rifampicin 300 mg orally every 12 hours for 2 months. She recovered well and there was no bacterial growth in repeated blood cultures.

Discussion

Vancomycin is the drug of choice for invasive MRSA infection. Due to the high mortality rate associated with MRSA infections, many alternative agents and combination