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CASE REPORT

Lemierre syndrome complicating multiple brain abscesses caused by extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* cured by fosfomycin and meropenem combination therapy

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A woman aged 56 years of age had a community-acquired left neck abscess and internal jugular vein thrombosis with septicemia due to extended-spectrum β-lactamase (ESBL)—producing *Klebsiella pneumoniae*. Even though she was treated with intravenous meropenem, the bacteremia persisted. She was complicated with multiple brain abscesses, seizure, and leucopenia. After a combination of intravenous fosfomycin and meropenem, her clinical condition became stable. Combination treatment was continued for 2 months and she recovered. In individual cases of Lemierre syndrome with brain abscess caused by ESBL-producing *Enterobacteriaceae*, fosfomycin combination therapy may be the alternative choice.

Introduction

Infections of the central nervous system (CNS) are critical medical emergencies and require the administration of antibiotics that are effective against resistant pathogens.

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Lemierre syndrome is characterized by septicemia, internal jugular vein (IJT) thrombosis, and metastatic septic emboli secondary to acute pharyngeal infections.[1] *Fusobacterium* species is the most common cause, and *Klebsiella pneumoniae* is rarely reported in the literature.[1,2] The lung is the most common site for metastatic infections (79.8% of cases).[3] In contrast, metastatic infections involving the CNS are rare. The successful treatment of multiple diffuse brain abscesses depends on an appropriate choice of antimicrobial agents, particularly in patients who did not receive surgical intervention.

Fosfomycin is a bactericidal antimicrobial agent with high antibacterial activity against variable gram-positive and gram-negative bacteria, especially multidrug-resistant (MDR) pathogens.[4] Fosfomycin had been proven to reach effective concentrations in the cerebral-spinal fluid (CSF) and brain tissue.[5,6] Here we report the first case of Lemierre syndrome complicating a diffuse brain abscess caused by extended-spectrum β-lactamase (ESBL)-producing *K pneumoniae* that was successfully treated by intravenous (IV) fosfomycin and meropenem combination therapy.

Case report

A previously healthy woman aged 56 years was admitted to our hospital with a 7-day history of fever, left neck swelling, and headache. On admission, consciousness was clear and her temperature was 39.4°C. Her body weight was 68 kg with moderate nutrition. Physical examinations showed a huge mass about 12 × 8 cm in size with local heat, erythema, and tenderness of left neck. White blood cell count was 17,200/mm^3 with 86% neutrophils. Serum level of C-reactive protein was 33.5 mg/dl, and serum creatinine 0.8 mg/dl. Chest X-ray and urinalysis were normal. Computed tomography of the neck revealed left neck abscess and IJT thrombosis (Fig. 1A). She received surgical debridement of the left neck abscess on the second day of hospitalization and empirical therapy with IV ceftazidime (2 g every 8 h) and metronidazole (500 mg every 6 h) was administered.

On the fourth day of admission, pus and blood cultures grew *K pneumoniae*. Since she had seizures and vomiting, antimicrobial therapy was shifted to IV ceftriaxone (2 g every 12 h) and amikacin (375 mg every 12 h). Brain magnetic resonance imaging (MRI) with gadolinium enhancement (Fig. 1B) showed multiple brain abscesses. The patient and family declined craniotomy and debridement because of a high risk of severe sequelae.

On the fifth day of admission, the susceptibility study revealed that *K pneumoniae* exhibited the ESBL phenotype. For *K pneumoniae* isolate, minimal inhibition concentration (MIC) of fosfomycin was ≤32 μg/ml and meropenem MIC ≤ 1 μg/ml by microdilution method, then antibiotic therapy was shifted to IV meropenem monotherapy (10 g every 8 h). The patient remained febrile, but complained of a headache. ESBL-producer bacteremia persisted after IV meropenem treatment for 1 week, so IV fosfomycin (4 g every 8 h) was supplemented. After the combination regimen of IV fosfomycin and meropenem, blood cultures became sterile and fever subsided. Combination treatment was continued for two months without apparent toxicity. The patient had no further evidence of metastatic infections or neurologic sequelae. A follow-up brain MRI at 1 month after discharge showed resolution of brain abscesses.

Discussion

The CNS is rarely involved in metastatic infection in patients with Lemierre syndrome, probably because the cerebral veins are the upstream from the septic thrombi in the IJT.[7,8] Because the patient did not receive craniotomy to debride the brain abscesses, the most important strategy for our patient with severe brain infections was the administration of antibiotics to achieve effective concentrations in the CSF and brain tissue.[9] The development of β-lactam resistance due to ESBL in *K pneumoniae* in the community-acquired infections had increasingly emerged in recent years.[10] So, the choice of appropriate antibiotics for MDR pathogens is a critical issue in the modern era of antibiotic resistance.

In a recent study about pharmacokinetic/pharmacodynamic characters of fosfomycin by Pfausler et al,[11] its bactericidal activity against methicillin-susceptible *Staphylococcus aureus* isolates causing the ventriculitis was time-dependent. In contrast, the bactericidal activity of fosfomycin against *Enterobacteriaceae* is concentration-dependent.[12] Both meropenem and fosfomycin can block bacterial cell wall synthesis, but they work on different steps of cell wall synthesis.[13] Fosfomycin in combination with meropenem for *K pneumoniae* revealed *in vitro*

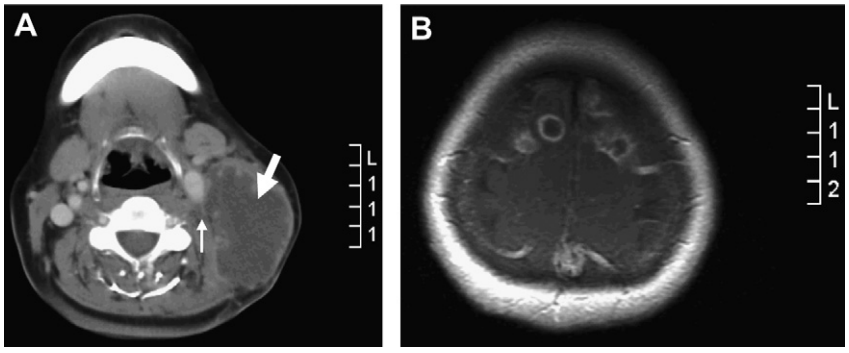

Figure 1. (A) contrasted computed tomography scan revealed a huge subcutaneous abscess (thick arrowhead) of the left neck with IJTthrombosis (thin arrowhead), (B) magnetic resonance imaging scan revealed multiple brain abscesses.

synergistic activity in the time-killing assays or by checkerboard method.[14] Fosfomycin was a hydrophilic antibiotic with small molecular weight, can penetrate the blood-brain-barrier (BBB), and achieve sufficient concentrations to exert a significant antimicrobial effect.[5,6,9] Fosfomycin combined with lipophilic antimicrobial agents, such as the fluoroquinolones, appears to effectively penetrate the BBB, even when the inflamed meninges has been recovered and healed. The simultaneous administration of β-lactams with fosfomycin has currently been demonstrated to have synergistic effects *in vitro*.[15] However, fosfomycin is suggested to be administered in combination with other classes of antimicrobial agents to avoid the development of bacterial resistance.[16]

To our knowledge, this patient is the first reported case of Lemierre syndrome complicated by multiple brain abscesses due to ESBL-producing *K pneumoniae* and who was successfully treated by fosfomycin combination therapy. In individual cases of brain abscesses caused by ESBL-producing *Enterobacteriaceae* pathogens, fosfomycin combination therapy may be the alternative choice.

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