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CASE REPORT

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A case report of brain abscess caused by carbapenem-resistant *Klebsiella pneumoniae*

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ABSTRACT

The treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) strains is difficult due to the limited antimicrobial options and high mortality. There are many reports on intracranial infections caused by CR-Kp, but only a few on brain abscesses caused by CR-Kp. Here, we present a case of brain abscess caused by CR-Kp successfully treated with combined antibiotics. A 26-year-old male patient was admitted to our hospital due to high fever and headache. His past medical history includes a surgical intervention due to an acute subdural hematoma, performed at an external healthcare center. After the current diagnosis of cerebral abscess, he underwent two surgeries. During the procedure, multiple cerebral abscesses were drained and capsulotomies were performed under ultrasound guidance. The combination of meropenem and vancomycin was started. The contents of the abscesses were sent to the microbiology and pathology laboratory. On the 3rd day of treatment, the medical team was informed that CR-Kp grew in an abscess culture. The patient's treatment was changed to meropenem + colistin + tigecycline. The patient developed electrolyte disturbances during the follow-up and this was considered an adverse effect of colistin. On the 41st day of treatment, colistin was discontinued, fosfomycin was added, and meropenem and tigecycline were maintained. Treatment was discontinued on the 68th day, when the patient was discharged. The general condition of the patient, who has been followed up for two years, is satisfactory. The treatment of CR-Kp infections should be individualized, and the pharmacokinetics and pharmacodynamics of antibiotics should be considered in each case.

KEYWORDS: *Klebsiella pneumoniae.* Carbapenem resistance. Brain abscesses.

INTRODUCTION

Multidrug-resistant gram-negative bacteria are being reported at increasing rates in many countries around the world. Isolates containing extended-spectrum beta-lactamase (ESBL) and carbapenemase enzymes show a high prevalence, especially in developing countries, due to overuse and misuse of antibiotics. Carbapenem-resistant Enterobacterales (CRE) is an important threat to public health due to their global spread[1-3].

Klebsiella pneumoniae is the most common isolated nosocomial pathogen among carbapenem-resistant gram-negative bacteria that is frequently isolated from intensive care patients and can cause epidemics with high mortality rates[4,5]. The management of CR-Kp is complex due to various mechanisms that mediate carbapenem resistance. It has been reported that treatment failure is higher in patients receiving monotherapy than in patients receiving combination therapy. Therefore,

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combinations with polymyxin E (colistin), tigecycline, and fosfomycin with carbapenems are recommended. It is stated that carbapenem combination results are better if the carbapenem minimum inhibitory concentration (MIC) value is ≤ 8 µg/mL[6]. Although new agents show promise in treatment, more data are needed for their empirical use. The most common CR-Kp infections are pulmonary, urinary tract, and bacteremia infections. There are many cases where CR-Kp is the causative agent as central nervous system involvement has been reported, but only a few cases of brain abscesses in which CR-Kp is the causative agent are reported in the literature[5,7,8]. Here, we present a case of brain abscess, the third case in the literature, in which CR-Kp was the causative agent and was successfully treated with combination therapy.

CASE REPORT

A 26-year-old male patient underwent his second operation with a diagnosis of brain abscess after an acute subdural hematoma operation at an external healthcare center. The patient was sent to our hospital for surgery with a diagnosis of a brain abscess after the second operation, due to a high fever and headache. After the dura was opened, multicentric abscess drainage and capsulotomy were performed with the use of ultrasound and microsurgical technique. The patient showed extensive osteomyelitis in the bone flap and discoloration of the dura during the surgery (Figure 1). The treatment with meropenem (3x2 g, IV) and vancomycin (2x1 g, IV) was initiated empirically. The abscess material taken during the operation was sent to the microbiology and pathology laboratory. It was reported that CR-Kp had grown in the abscess culture on the 3rd day of treatment. Antimicrobial drug susceptibility testing was performed by the disc diffusion and microdilution methods. The meropenem MIC value of the bacteria was ≥ 16 µg/mL and the colistin MIC value was 1 µg/mL. This strain was resistant to all antibiotics except colistin, amikacin, tigecycline, and trimethoprim-sulfamethoxazole. After the antimicrobial susceptibility results were reported, the patient's treatment was arranged as meropenem (3x2 g, IV) + colistin (4x150 mg, IV) + tigecycline (1x100 mg, after IV loading dose 2x50 mg, IV). In the early postoperative period, it was observed on MRI that the hypointense image within the loch and the surrounding contrast decreased. In the report sent to pathology, it stated that tissue fragments containing abscess areas were observed in the right parietal lobe. It was thought that the electrolyte disturbances (hypomagnesemia, hypophosphatemia, hypocalcemia, and hypopotassemia) that caused unconsciousness during the follow-up could have been due to colistin. On the 41st day of treatment, colistin was discontinued, fosfomycin (4x4 g, IV) was added, and meropenem and tigecycline were maintained. The abscess site was significantly reduced and the peripheral edema and contrast were significantly reduced in the MRI taken during the 2nd month postoperatively. The patient, whose treatment was discontinued on the 68th day (fosfomycin on the 28th day), was discharged. The general condition of the patient, who has been followed up for two years, is good. Encephalomalacia areas in the right frontoparietal were observed in the MRI taken in the 3rd month after the completion of the treatment. MRI findings after surgery are shown in Figure 2.

DISCUSSION

Carbapenem-resistant *K. pneumoniae* (CR-Kp) is an important threat to public health with its global spread and high mortality. CR-Kp growth in hospitals is considered an independent risk factor for mortality. The use of broad-spectrum cephalosporins and/or carbapenems is an important predisposing factor for the development of

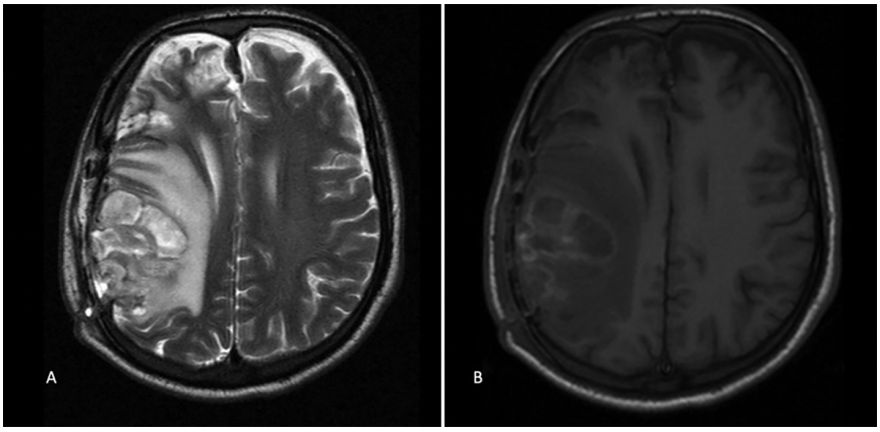

Figure 1 - MR images of the patient before surgery: A and B) T2 sequence axial image demonstrating multilobular hemispheric edema and shifted abscess.

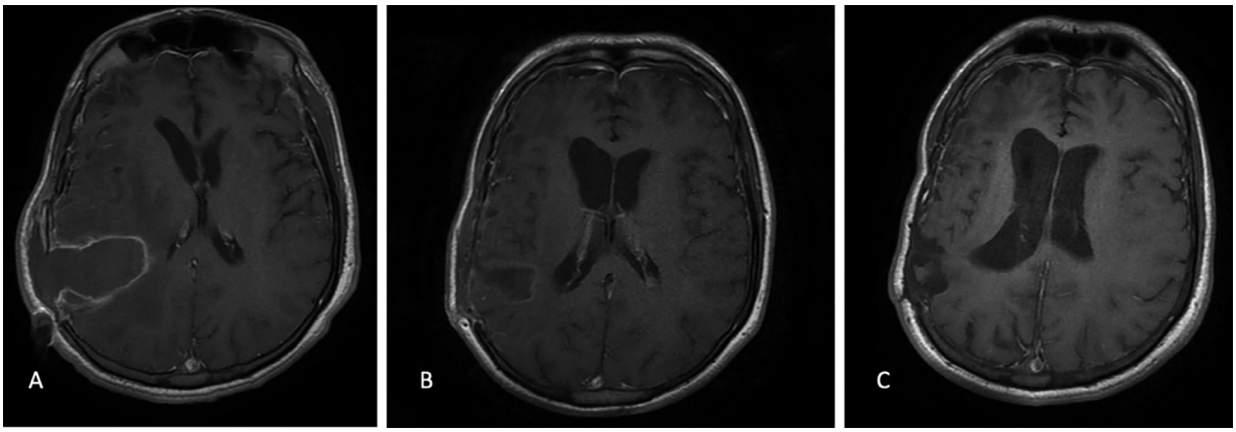

Figure 2 - Axial images with contrast T1 sequence after surgery; T1 sequence image demonstrating that the abscess disappeared: A) image from September 30, 2019; B) image from October 26, 2019; C) image from May 19, 2022.

colonization or infection with multidrug-resistant pathogens such as CR-Kp. Trauma, diabetes mellitus, malignancy, organ transplantation, mechanical ventilation, use of urinary catheters, and central venous catheters are associated conditions for colonization with a carbapenemase-producing microorganism. The most common CR-Kp infections are pulmonary, urinary tract, and bacteremia infections[1,4,5].

The management of infections caused by CR-Kp is not clearly defined and antibiotic options are limited. These antibiotics include aminoglycosides, colistin, tigecycline, and fosfomycin. Aminoglycosides and colistin have poor safety profiles due to their nephrotoxic effects. Tigecycline has an unfavorable pharmacokinetic profile due to its rapid and high passage from blood to tissues, and association with increased mortality. New β-lactamase inhibitors (e.g., avibactam and vaborbactam) have changed the management of CR-Kp infections. However, these new β-lactamase inhibitors are not active against all major carbapenemases[2,6,9,10].

Prior to the use of new β-lactam/-lactamase inhibitor combinations (ceftazidime/avibactam or meropenem/vaborbactam), combination therapies were reported to have better clinical success and lower mortality rates than monotherapy. In this sense, colistin-based combination therapies have been predominantly used. Combinations with a double carbapenem (ertapenem plus meropenem) or colistin or tigecycline have been investigated in several studies[6]. Treatment failures were significantly higher in patients receiving monotherapy (49% vs 25%; p = 0.01), and treatment failure rates were higher in patients receiving polymyxin therapy alone than in patients receiving polymyxin-based combination therapy (73%)[11]. Patients receiving carbapenem monotherapy had higher rates of treatment failure (26% versus 60%; p = 0.03) when compared to carbapenem-based combination therapy. In addition, some studies have observed lower rates of mortality with carbapenem-based combination therapy compared with non-carbapenem-based combination therapy. The efficacy of carbapenem combination therapy also appears to be MIC-dependent. It has been reported that treatment results are better if the carbapenem MIC value is < 8μg/mL[11]. Combination regimens may be beneficial in the treatment of CR-Kp infections, but the evidence for the efficacy of combination regimens comes from retrospective and observational case series, so it is difficult to determine which regimens are more effective[12].

Staphylococci and gram-negative bacilli are the most common pathogens of central nervous system infections after neurosurgical procedures. Infections caused by multi-drug-resistant gram-negative bacilli are increasing[13,14]. Most importantly, CR-Kp has become a global threat. Infections caused by CR-Kp have a high mortality rate of up to 40–50%[4]. The epidemic characteristics of CR-Kp meningitis cannot be described due to the small number of reports. Marmer *et al.*[15] reported that a case of CR-Kp meningitis developed following cerebellar infarction and ventriculoperitoneal shunt (VPS) placement was treated with intravenous polymyxin E and VPS removal. Emiroglu *et al.*[9] reported that a 5-month-old boy with ventriculoperitoneal shunt infection was cured after shunt removal, intravenous tigecycline and meropenem, and intrathecal amikacin. Holyk *et al.*[10] demonstrated the effectiveness of ceftazidime/avibactam administration in the treatment of CR-Kp meningitis. Chen *et al.*[7] reported that they successfully treated a patient who developed meningitis and a brain abscess caused by CR-Kp, using intrathecal amikacin with drainage, tigecycline + amikacin, and trimethoprim-sulfamethoxazole. Pektezel *et al.*[8] reported that they successfully treated a case of CR-Kp meningitis and brain abscess with ceftazidime-avibactam. In our case, the patient's treatment was arranged as meropenem +

colistin + tigecycline. It was thought that the electrolyte disturbance that had developed during this treatment may have been due to colistin. Colistin was discontinued on the 41st day of treatment, fosfomycin was added, and meropenem and tigecycline were maintained. The patient was discharged on the 68th day of the total treatment (fosfomycin, 28th day) to be followed up as an outpatient. The general condition of the patient, who has been followed up for two years, is good.

CONCLUSION

The treatment of CR-Kp infections should be individualized on a patient basis, and the pharmacokinetics and pharmacodynamics of antibiotics should be considered in each case. Carbapenems may still be an option for treatment. Here, we present a case that was successfully treated with a triple-drug regimen consisting of a high dose of carbapenem with a long-term infusion (e.g., meropenem), combined with colistin (later fosfomycin) and tigecycline.

AUTHORS' CONTRIBUTIONS

TT and EI: data collection, text writing, and review of the literature; CK, BS and AG: text editing and review of the literature.

CONFLICT OF INTERESTS

The authors have no conflict of interests to disclose.

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