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CASE REPORT

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Post-neurosurgical meningitis caused by KPC-producing *Klebsiella pneumoniae*: report of two cases

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ABSTRACT

Nosocomial bacterial infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is associated with high mortality in neurosurgical patients. There are few reports in the literature on meningitis caused by CRKP. We report two cases of CRKP meningitis after neurosurgery. The *K. pneumoniae* identification and antimicrobial susceptibility testing were performed using the Vitek Compact System. Minimum inhibitory concentrations of polymyxin B were determined using the broth microdilution method. Molecular typing of *K. pneumoniae* isolates was investigated using multilocus sequence typing. Antimicrobial susceptibility testing showed that the *K. pneumoniae* isolates were multidrug resistant and co-produced extended-spectrum β-lactamases and KPC enzymes. The patients were treated with intrathecal polymyxin. Genetic polymorphism analyses revealed two different *K. pneumoniae* clones (ST1298 and ST2687), which were observed for the first time in CRKP infections. We recommend intravenous administration of intrathecal polymyxin for treating meningitis caused by multidrug-resistant *K. pneumoniae*.

KEYWORDS: Meningitis. *Klebsiella pneumoniae*. Carbapenem-resistant. Beta-lactamases. Cerebrospinal fluid.

INTRODUCTION

Meningitis refers to several infections defined as inflammation of the meninges; it may be caused by various infectious agents, including bacteria, viruses, parasites, fungi and non-infectious processes. Although viral meningitis is the most common, bacterial meningitis may be more severe and potentially life-threatening[1]. In recent years, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has become endemic and is one of the biggest public health concerns globally[2,3]. However, there are few reports in the literature on meningitis caused by CRKP[4,5]. We report two cases of post-neurosurgical nosocomial meningitis due to CRKP that were successfully treated with polymyxin.

MATERIALS AND METHODS

Clinical data were obtained from medical records. Bacterial identification and antimicrobial susceptibility testing were performed using the Vitek 2 Compact System® (bioMérieux, Marcy L'Étoile, France). The polymyxin B minimum

inhibitory concentrations (MICs) were determined using the reference Clinical Laboratory Standards Institute broth microdilution method[6]. Genes coding for extended-spectrum β-lactamases (*bla*-$_{CTX-M}$, *bla*-$_{TEM}$, *bla*-$_{SHV}$), carbapenemases (*bla*-$_{KPC}$, *bla*-$_{OXA-48}$), and metallo-β-lactamases (*bla*-$_{NDM-1}$, *bla*-$_{IMP}$, *bla*-$_{VIM}$) were investigated using the polymerase chain reaction, as described previously[7-9]. Molecular typing was performed by multilocus sequence typing (MLST)[10].

CASE REPORTS

Case 1

A 17-year-old man from Campo Grande, Mato Grosso do Sul State, Brazil, was admitted to the emergency room after a car accident. On admission, the patient was sedated and intubated and had a heart rate of 90 beats/min, respiratory rate of 17 breaths/min, arterial blood pressure of 160/90 mmHg, Glasgow Coma Scale (GCS) score of 3/15 and APACHE index of 17. The skull computed tomography (CT) revealed cerebral edema with post-traumatic hydrocephalus, frontal lobe contusion and subarachnoid hemorrhage (grade IV on the Fisher scale).

An external ventricular shunt was inserted. The patient developed anisocoria and miotic pupils. Besides diffuse edema noted on a new CT, decompressive craniotomy was necessary. He also underwent various invasive procedures during hospitalization, including tracheostomy, central venous catheterization, urinary catheterization, enteral nutrition and mechanical ventilation. On postoperative day 3, the patient developed septic shock, probably from skin and fascial breast foci. Cerebrospinal fluid (CSF) examination revealed no abnormalities (Table 1). However, head CT revealed opacification of the left maxillary and ethmoidal sinuses. Intravenous (IV) meropenem, 1 g/8 h was administered. Clinical improvement and of the consciousness level was noted (GCS 8). On hospitalization day 11, his level of consciousness deteriorated again (GCS score decreased to 3/15); he presented with hyperthermia (38.8 ºC), arterial hypertension (153/90 mmHg), and leukocytosis (leukocytes 39,600/mm³, with 84% segmented and 4% rods). New CSF analysis showed lymphocytic pleocytosis that was culture positive to *K. pneumoniae*, which was resistant to most antibiotics tested, including all β-lactams and gentamicin. However, it was susceptible to amikacin, ciprofloxacin and polymyxin (MIC=0.25). Analysis of β-lactamase genes revealed the presence of *bla*-$_{TEM}$, *bla*-$_{SHV}$, and *bla*-$_{KPC}$ genes. The isolate was identified as sequence type 1298.

Because of his clinical condition and decreasing consciousness level, IV polymyxin E 150 mg/12 h was added to his treatment for 19 days. Meropenem was maintained following CSF culture results, with the dose increased to 2 g/8 h. Despite improved CSF parameters, intrathecal polymyxin E (5 mg/day for 3 days and then every other day to complete 7 days of treatment) was introduced. The patient was discharged 37 days after admission with a GCS score of 15 and no CSF abnormalities (Table 1).

Table 1 - Case 1 cerebrospinal fluid characteristics compatible with an acute bacterial meningitis caused by a KPC-producing *K. pneumoniae.*

Parameters	Hospitalization day			
	3	11	21	36
White blood cell (mm³)	6	21,000	40	1
Red blood cell (mm³)	800	800	45	3
Neutrophils (%)	-	04	95	-
Lymphocytes/Monocytes (%)	-	96	5	-
Proteins (mg/dL)	10	1,336	75	37
Glucose (mg/dL)	77	10	41	52

Case 2

A 50-year-old woman from Sao Gabriel do Oeste, Mato Grosso do Sul State (MS), Brazil, presented with severe traumatic brain injury and loss of consciousness after a fall from her own height. The Emergency Mobile Care Service classified the patient as having a severe condition with a cephalic contusion of 3 cm, GCS score of 7/15, anisocoric pupils, normal blood pressure (110/70 mmHg) and normal cardiopulmonary auscultation. She had a history of mental disorder due to cerebral palsy, arterial hypertension and diabetes mellitus.

The patient was transferred to a tertiary hospital in Campo Grande, MS. On admission, she was sedated and intubated after first aid. She had a GCS score of 4/15, isochoric pupils, lack of motor response, hypotension, heart rate of 130 beats/min and no respiratory abnormalities. Cranial CT showed subarachnoid hemorrhage with left frontal hematoma, cerebral edema and intracranial hypertension. She was classified as grade 4 on the Fisher scale for subarachnoid hemorrhage and underwent an external ventricular derivation surgery. On hospitalization day 4, the patient developed pneumonia. The chest radiograph showed opacity in the right lower lobe of the lung. Intravenous piperacillin/tazobactam 0.5 g plus4 g/6 h and IV linezolid 600 mg/12 h were administered for 7 and 10 days respectively, to treat the nosocomial pneumonia. After hospitalization day 16, fever developed (38.8 °C). Because her clinical condition worsened, IV polymyxin

E 150 mg/12 h for 7 days and IV meropenem 1 g/8 h for 9 days were initiated. Intrathecal polymyxin E (5 mg/day for 3 days, followed by its use on every other day to complete 14 days of treatment) was administered because fever and GCS score of 3/15 persisted. This medication was introduced based on CSF results on day 18 (Table 2). CSF analysis showed pleocytosis with neutrophil predominance and *K. pneumoniae* grew on culturing. Antimicrobial susceptibility testing showed sensitivity to amikacin, gentamicin and polymyxin B (MIC=0.5 µg/mL) and resistance to all β-lactam antibiotics. *K. pneumoniae* harbored *bla-*$_{CTX-M}$, *bla-*$_{SHV}$, and *bla-*$_{KPC}$ genes. The strain belonged to clone ST 2687 in MLST. Due to favorable clinical and laboratory results, after hospitalization day 46, the patient was transferred to a hospital in Sao Gabriel do Oeste, MS, so that we do not have further information about her.

Table 2 - Case 2 cerebrospinal fluid characteristics compatible with an acute bacterial meningitis caused by a KPC-producing *K. pneumoniae.*

Parameters	Hospitalization day		
	11	18	22
White blood cell (mm³)	8	1,100	73
Red blood cell (mm³)	1,230	12,160	420
Neutrophils (%)	-	73	78
Lymphocytes/Monocytes (%)	-	27	22
Proteins (mg/dL)	248	462	233
Glucose (mg/dL)	58	21	38

DISCUSSION

Nosocomial bacterial meningitis, especially carbapenem-resistant intracranial bacterial infections, are life-threatening complications in neurosurgical patients[11,12]. The most frequent causative agents of health-care-associated meningitis are *Staphylococcus* spp. and multidrug-resistant and extensively drug-resistant gram-negative bacteria, including *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli* and *K. pneumoniae*[13]. *K. pneumoniae* causes several nosocomial infections. The most common sites of CRKP infection are the respiratory system, urinary tract and bloodstream. CRKP is rarely isolated from CSF samples[4,5,14].

Meningitis caused by CRKP post-neurosurgery has been reported in many countries, including Turkey[15], USA[5] and China[16]. In Brazil, Tuon *et al.*[17] described for the first time a nosocomial KPC-producing *K. pneumoniae* meningitis in the South region. To our knowledge, these are the first CRKP meningitis cases described in the Midwest of Brazil. Invasive procedures, including mechanical ventilation and central venous catheterization are associated with the acquisition of multi-resistant bacteria. Surgery is a risk factor for CRKP infections[16]. Infections after head trauma, similar to our cases, followed by neurosurgical procedures and gram-negative meningitis/ventriculitis, have been reported[11].

Diagnosis of meningitis can be difficult. CSF cultures are the most important test to diagnose healthcare-associated ventriculitis and meningitis[13]. Although bacteriological CSF cultures from Case 1 on day 11 indicated CRKP and CSF parameters were consistent with meningitis, lymphocytosis was initially present. Lymphocytosis may be present as a component of acute bacterial meningitis mainly in neonatal and pediatric patients[18,19]. The emergence of CRKP infections is a rising public health threat associated with extremely high morbidity and mortality rates that demand caution with antibiotic use[12,16].

In our two cases, we observed *K. pneumoniae* isolates co-producing extended-spectrum β-lactamases (ESBLs) and KPC enzymes. ESBLs of TEM, SHV and CTX-M types are very common among *Klebsiella* spp[9]. ESBL-producing *K. pneumoniae* may be more invasive and resistant and the distribution of these bacteria varies according to geographical areas[20]. CRKP is already endemic in many countries, including Brazil. This mechanism confers a high resistance to β-lactams, including carbapenems[3,20]. A study conducted in Mato Grosso do Sul State reported a high rate (93.3%) of CRKP in that region[21]. Genetic polymorphism analyses of the two *K. pneumoniae* isolates revealed two different clones: ST1298 and ST2687. In Brazil, sequence types ST11, ST437, and ST340 are more frequently reported among *K. pneumoniae* isolates, while ST258 are the most frequently associated with KPC enzyme production in Europe and the USA[22]. Here, we report for the first time the involvement of ST1298 and ST2687 in meningitis caused by CRKP. Treatment of central nervous system infections is more limited than those of bloodstream and pulmonary infections. There are limited data on optimal dosing and brain barrier penetration of most agents administered to treat carbapenem-resistant *Enterobacteriaceae* infections[6,23].

CRKP infections are treated with combination therapies, including polymyxin or tigecycline with carbapenems, aminoglycosides, fluoroquinolones or fosfomycin[22]. A high carbapenem MIC (MIC ≥8µg/mL) predicts a lower response to the antibiotic[23]. The relatively new antimicrobial ceftazidime-avibactam (approved in 2014 by the U.S. Food and Drug Administration, USA) has been successfully used for treating CRKP meningitis. The drug is less toxic and can inhibit KPC-2 carbapenemase and group C beta-lactamases[5]. Ceftazidime-avibactam has a great treatment

potential because of its direct action on the carbapenem resistance mechanism. However, this option was not available for the reported cases. Although intravenous polymyxins poorly penetrate the CSF and they present with high pharmacokinetic variability, the combination of intravenous polymyxin E and intrathecal polymyxin showed satisfactory responses with resolution of meningitis[23].

We reported two rare cases of meningitis caused by CRKP that were satisfactorily treated with intravenous polymyxin and intrathecal polymyxin, despite the associated high mortality reported in literature.

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AUTHORS' CONTRIBUTIONS

YCP and LPT reviewed medical records; ACSR and ICOS conducted the genetic experiments; GSC and GARB were responsible for samples collection, strain isolation and identification; CEVC reviewed the clinical cases; APDCA and MRC contributed for the manuscript writing.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICAL APPROVAL

This study was approved by the ethics committee (CAAE - 50087815.2.0000.0021).

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