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Case Report

Successful treatment of meningitis caused by multidrug-resistant *Acinetobacter baumannii* with intravenous and intrathecal colistin

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Multidrug-resistant *Acinetobacter baumannii* is an emergent nosocomial pathogen. A 61-year-old woman developed meningitis caused by MDRAB 27 days after receiving a surgical intervention for invasive meningioma. The patient failed to respond to high doses of meropenem and sulbactam treatment and the organism persisted in the cerebrospinal fluids for two months. The regimen was changed to intravenous and intrathecal colistin for 28 days and the patient responded well. Administration of colistin both intravenously and intrathecally could be a suitable option as a salvage therapy for meningitis due to multidrug-resistant *A. baumannii*.

***Key words*:** *Acinetobacter baumannii*; Colistin; Drug resistance, multiple; Injections, spinal; Meningitis, bacterial

Introduction

Multidrug-resistant *Acinetobacter baumannii* (MDRAB) has gradually increased in importance as a nosocomial pathogen. Strains that are resistant to all available antimicrobials agents in clinical practice, including aminoglycosides, cephalosporins, fluoroquinolones, carbapenems and beta-lactamase inhibitors, are increasingly encountered. Treatment of these organisms is challenging since the choice of antibiotics is limited, and management becomes even more difficult if the clinical picture involves meningitis. We present a case of post-neurosurgical meningitis involving MDRAB that was unresponsive to carbapenem plus sulbactam, but resolved after treatment was switched to colistin.

Case Report

A 61-year-old woman was first admitted to our hospital in September 2003 with a primary complaint of weakness in her right leg. An enormous out-bulging mass in the left parietal area was noted on computed tomography. The tumor was removed in September 2003 and the pathology assigned as invasive meningioma. In March 2006, the tumor recurred with 2 masses palpable in the scalp of the right parietal area. On the seventh hospital day, she underwent craniectomy for tumor removal and cranioplasty with brain cement. On day 11 of hospitalization, her consciousness was abruptly disturbed and follow-up computed tomography showed swelling in the left parietal lobe. Emergent craniectomy was performed to release pressure on the brain, and a dura patch was used for duraplasty. On day 27 of hospitalization, the patient received right hemicolectomy due to 2 anorectal ulcers with active bleeding despite suture ligation. On day 28 of hospitalization, external lumbar drainage was inserted to relieve the intracranial pressure. After this intervention, the patient developed fever of 38.5°C and unstable blood pressure. After ruling out other sources of infection, the artificial dura graft was suspected to be an infection focus. On day 34 of hospitalization, the artificial graft was removed and replaced by lata fascia taken from her right thigh. The external lumbar drainage was removed and an external

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Table 1. Summary of antibiotic treatment and laboratory data in a patient with multidrug-resistant *Acinetobacter baumannii* meningitis (day 28 to 76)

Variable	Day of admission						
	28	34	49	62	65	69	76
CSF glucose (mg/dL)	24	117	56	26	60	59	6
CSF protein (mg/dL)	345	39	28	158	109	65	112
CSF cell count (μL)	2910	210	20	440	82	200	243
PMN (%)	90	82	36	50	11	0	51
Lym (%)	1	1	33	33	76	86	36
Culture	No growth	*A. baumannii*	*A. baumannii*	*A. baumannii*	*A. baumannii*	*A. baumannii*	*A. baumannii*
Antibiotics	Ox IV 2 g q6h + Fl IV 2 g q8h (day 23-28) switched to Te IVD 400 mg qd + Fl IV 2 g q8h (day 28-31)	Me 2 g IV q8h (day 31-63) + Su 1 g IV q8h (day 39-63)			Co IV 2 million IU q8h (day 63-84)		

Abbreviations: CSF = cerebrospinal fluid; PMN = polymorphonuclear cells; Lym = lymphocytes; Ox = oxacillin; IV = intravenous; q6h = every 6 h; Fl = flomoxef; q8h = every 8 h; Te = teicoplanin; IVD = intravascular device; qd = once a day; Me = meropenem; Su = sulbactam; Co = colistin

ventricular drain was inserted. Three days later, cerebrospinal fluid (CSF) culture obtained during the surgery grew *A. baumannii*. The CSF data are shown in Table 1 and Table 2. The identified pathogen was resistant to all the antibiotics examined in the laboratory by disk diffusion susceptibility test, including carbapenems, cephalosporins, fluoroquinolones, aminoglycosides and aztreonam. The patient received intravenous meropenem 2 g every 8 h and sulbactam 1 g every 8 h for 30 days due to the fact that a substitution was unavailable. She had intermittent fever and CSF culture performed once per week continued to grow *A. baumannii*. All of the pathogens isolated had identical antibiograms. We started colistin 2 million IU intravenously every 8 h from day 63 of hospitalization. CSF culture continued to grow *A. baumannii* after 3 weeks of colistin administration. The external ventricular drain was revised on day 94.

Table 2. Summary of antibiotic treatment and laboratory data in a patient with multidrug-resistant *Acinetobacter baumannii* meningitis (day 93-155)

Variable	Day of admission										
	93	97	99	100	101	104	118	121	125	128	155
CSF glucose (mg/dL)	4	<0.4	NA	NA	31	60	60	64	58	51	54
CSF protein (mg/dL)	71	190	NA	NA	108	165	70	182	79	109	35
CSF cell count (μL)	1980	4230	NA	NA	60	700	102	50	35	58	8
PMN (%)	91	97	NA	NA	92	57	0	0	1	0	45
Lym (%)	1	1	NA	NA	6	27	92	73	92	66	39
Culture	*A. baumannii*	*A. baumannii*	NA	NA	No growth	No growth	No growth	*A. baumannii*	*A. baumannii*	No growth	No growth
Antibiotics	Me IV 2 g q8h + Su IV 1 g q8h (day 84-98)		Co IT 20,000 IU q24h + Co IV 2 million IU q8h (day 99)	Co IT 40,000 IU q24h + Co IV 2 million IU q8h (day 100)	Co IT 60,000 IU q24h + Co IV 2 million IU q8h (day 101-102)	Co IT 30,000 IU q24h + Co IV 2 million IU q8h (day 103-113)	Co IT 60,000 IU q48h + Co IV 2 million IU q8h (day 114-126)			Co IT 80,000 IU q24h + Co IV 2 million IU q8h (day 127-155)	Discontinued Co on day 155

Abbreviations: CSF = cerebrospinal fluid; PMN = polymorphonuclear cells; Lym = lymphocytes; NA = not available; Me = meropenem; IV = intravenous; q8h = every 8 h; Su = sulbactam; Co = colistin; IT = intrathecal; q24h = every 24 h; q48h = every 48 h

On day 99 of hospitalization, intrathecal injection of colistin 20,000 IU per day was given through an external shunt. The daily dosage of intrathecal colistin was slowly increased to 60,000 IU in combination with intravenous colistin 2 million IU every 8 h. CSF culture was sterile on the second day of intrathecal therapy and remained sterile for the next 3 weeks. Nevertheless, *A. baumannii* reappeared when we reduced the dose of intrathecal colistin to 60,000 IU every 48 h. The intrathecal dosage was elevated to 80,000 IU every 24 h from day 127 of hospitalization. CSF culture was sterile on the next day and we removed the ventriculoperitoneal shunt that was concomitant with external ventricular drainage on day 135. A permanent ventriculoperitoneal shunt was inserted on day 155 after the CSF culture had been confirmed as remaining sterile for 4 weeks. The patient has been followed up for 6 months, with no evidence of relapse.

Discussion

A. baumannii is a Gram-negative, non-fermenting coccobacillus that is widespread in nature. It does not have fastidious growth requirements and is able to grow at various temperature and pH conditions [1]. *A. baumannii* survives in either moist or dry conditions in the hospital environment and has intrinsic resistance to many antimicrobial agents. These factors have contributed to the emergence of *A. baumannii* as a leading pathogens in nosocomial infections.

The presence of carbapenem-resistant *A. baumannii* was first reported in the United States in 1991 [2]. Since then, carbapenem-resistant *A. baumannii* infections and hospital outbreaks have been reported in many countries. Furthermore, a so-called MDRAB was first reported in Taiwan in 1998 [3]. MDRAB is resistant to almost all commercially available antibiotics, including carbapenems, cephalosporins, aztreonam, aminoglycosides and fluoroquinolones. MDRAB was first noticed in our hospital in 2002. We used combination therapy of carbapenem (imipenem or meropenem) with sulbactam, and the clinical response was fairly satisfactory. Nonetheless, the consequences can be grave when the infection involves meningitis.

Colistin is one of the polymyxin antibiotics produced by *Bacillus colistinus*. Polymyxins were discovered in 1947 and have been available since 1959 for the treatment of infections caused by Gram-negative bacteria [4,5]. However, early clinical reports noted a high incidence of nephrotoxicity and neurotoxicity

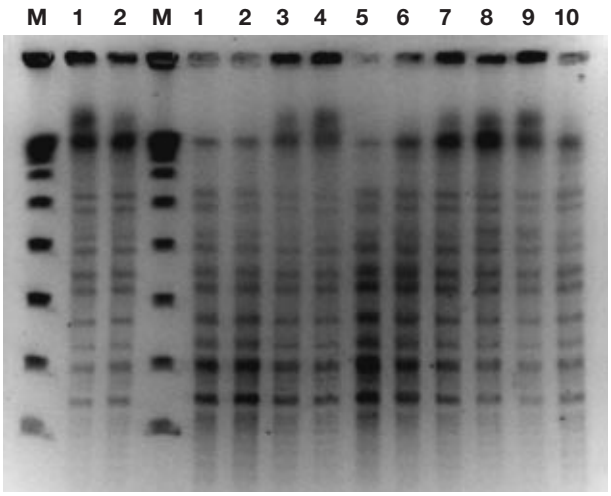

Fig. 1. Molecular typing of the cerebrospinal fluid *Acinetobacter baumanii* isolate by pulsed-field gel electrophoresis

associated with colistin. Colistin was thus abandoned and replaced by other less toxic antibiotics, such as beta-lactams. Nowadays, the emergence of multidrug-resistant Gram-negative pathogens has led to a resurgence in the use of polymyxin. The cationic polypeptide of colistin interacts with anionic lipopolysaccharide molecules in the outer membrane of Gram-negative bacteria, which leads to derangement of the cell membrane [6]. Polymyxins provide bacteriostatic activity at low concentrations, bactericidal activity at high concentrations and potent antiendotoxic activity [7,8].

At present, clinical articles on the intrathecal use of colistin are scarce. Variable doses of intrathecal colistin, ranging from 1.6 to 20 mg, have been used in different studies [9-13]. However, intrathecal administration of colistin 60,000 IU every 48 h failed to eradicate MDRAB in this case. Molecular typing by pulsed-field gel electrophoresis showed that serial CSF isolates were of the same clonal type (Fig. 1). Increasing the intrathecal colistin dose to 80,000 IU every 24 h and combining this with intravenous colistin 2 million IU every 8 h saw eventual resolution of the infection.

Generally, intrathecal or intraventricular administration of colistin has been well tolerated, except in 1 study, which reported development of numbness on the patient's left arm. The symptom subsided after the dose of intrathecal colistin was reduced [14].

From the case presented here, we propose that cases of meningitis caused by MDRAB could be treated with intrathecal colistin 80,000 IU per day in combination with intravenous colistin 2 million IU every 8 h. The combination therapy could be an effective alternative treatment.

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