IDCases 10 (2017) 135–137

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Recurrence of *Escherichia coli* meningitis in a preterm infant and co-infection of echovirus 18

Kentaro Kato[a], Hiroshi Mizumoto[a,*], Kousaku Matsubara[b], Atsuko Hata[a], Jun-ichi Wachino[c], Yoshichika Arakawa[c], Daisuke Hata[a]

[a] Department of Pediatrics, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan
[b] Department of Pediatrics, Nishi-Kobe Medical Center, Kobe, Japan
[c] Department of Bacteriology, Nagoya University Graduate School of Medicine, Nagoya, Japan

ARTICLE INFO

Keywords:
Bacterial meningitis
Escherichia coli
Recurrence
Echovirus 18
Preterm infant

ABSTRACT

Introduction: Bacterial meningitis may relapse after adequate antibiotic treatment. In most cases, however, the pathophysiology cannot be identified.
Presentation of case: We describe a preterm infant with recurrent episodes of meningitis due to infection with an identical *Escherichia coli* strain both at birth and at 10 days after cessation of a 3 week course of appropriate antibiotic treatment. At the time of recurrence, the patient presented with fulminant severe cardiac failure due to acute myocarditis, coupled with a concurrent echovirus 18 infection (confirmed by stool culture and serological analysis).
Conclusion: Co-infection by echovirus may underlie recurrence of *Escherichia coli* meningitis in this case.

Introduction

Despite advances in newborn intensive care, bacterial meningitis is a serious disease. *Escherichia coli* (*E. coli*) is the second most common pathogen for neonatal meningitis, after group B *Streptococcus*. Neonates with *E. coli* meningitis require treatment with parenteral antibiotics for 14 days after sterilization of cerebrospinal fluid (CSF), or for 21 days in total, whichever is longer [1]. However, meningitis may recur in very rare situations, for example, in cases with anatomic defects or immune deficiency.

Here, we report the case of a preterm infant who developed recurrent *E. coli* meningitis 10 days after cessation of a first round of 21 day antibiotic therapy. At the time of recurrence, the patient presented with clinical features suggestive of myocarditis concomitant with meningitis; also, co-infection with echovirus 18 was identified, suggesting a contribution to recurrence.

Methods

Isolates were subjected to antimicrobial susceptibility tests using the disk diffusion method. Two *E. coli* strains were isolated, and genomic DNA was analyzed using the MiSeq System (Illumina Inc.). Drug-resistant genotype, serotype, multilocus sequence type, and virulence genes were identified by comparison with databases at the Center for Genomic Epidemiology (www.genomicepidemiology.org).

Informed consent to publish was obtained from the patient's guardian.

Case

A male infant was born by vaginal delivery at 33 weeks of gestation (birthweight, 2190 g) after premature rupture of the membrane. The patient's mother suffered from intrapartum fever and was treated with ampicillin (ABPC) before delivery. The patient was asphyxiated at birth with Apgar scores 3 and 3 at 1 and 5 min, respectively, and required resuscitation with endotracheal intubation. Laboratory data revealed leukopenia and elevated C-reactive protein (CRP) levels (Table 1). CSF analysis revealed mild pleocytosis with elevated protein levels. Treatment with ABPC and cefotaxime (CTX) was initiated under a tentative diagnosis of sepsis (Fig. 1). On the next day, *E. coli* was isolated from blood and CSF samples obtained at birth. The strain was resistant to ABPC and CTX but susceptible to meropenem (MEPM) (Table 1). Based on the susceptibility test results and the poor response to initial treatment, we substituted ABPC and CTX with MEPM (100 mg/kg/day, divided into three doses). Thereafter, the patient's respiratory condition improved gradually. The patient received MEPM for 21 days. Blood cultures on Days 2, 7, and 16, and CSF cultures on Days 7 and 16, were all negative. Cranial magnetic resonance imaging (MRI) on Day 31

* Corresponding author at: Department of Pediatrics, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, 2-4-20, Ohgimachi, Kita-ku, Osaka, 530-8480, Japan.
E-mail address: h-mizumoto@kitano-hp.or.jp (H. Mizumoto).

https://doi.org/10.1016/j.idcr.2017.11.003
Received 23 August 2017; Received in revised form 6 November 2017; Accepted 6 November 2017

Table 1
Laboratory data.

	Reference	Day 0	Day 2	Day 7	Day 16	Day28	Day 32	Day 34	Day 63
Blood									
White blood cell ($\times 10^3$/μl)	3.9–9.8	2.5	5.4	26.6	13.1	8.7	3.8	3.4	5.1
Hemoglobin (g/dL)	13.5–17.6	19.3	14	15.4	12.3	13.2	12.6	13.5	12.5
Platelet ($\times 10^3$/μl)	131–362	128	104	307	475	522	522	52	188
C-reactive protein (mg/dL)	< 0.3	2.91	14.56	1.31	0.14	0.02	1.98	23.8	0.47
Creatinine kinase (IU/L)	59–249						102	415	69
Creatinine kinase isozyme-MB (IU/L)	< 25						40	37	17
Troponin-T (ng/mL)	< 0.045						0.28	< 0.012	
BNP (pg/mL)	< 18.4							572.1	28.7
HANP (pg/mL)	< 43							335	44.3
CSF									
Cell count		43	1717	1118	76			1189	102
polymorphonuclear cells (/μl)		2	1467	1018	9			1123	2
mononuclear cells (/μl)		41	250	100	67			66	100
Protein (mg/dL)	20–45	344	320	360	247			1430	1154
Glucose (mg/dL)	40–75	48	63	11	31			< 3	29

Antimicrobial susceptibility tests	Minimum inhibitory concentration (μg/ml)	
Ampicillin	> 16	Resistant
Piperacillin	> 64	Resistant
Cefazolin	> 16	Resistant
Cefotiam	> 16	Resistant
Cefotaxime	> 2	Resistant
Cefepime	0.25	Susceptible
Meropenem	0.25	Susceptible
Aztreonam	4	Susceptible
Moxifloxacin	0.5	Susceptible

Abbreviations: BNP; brain natriuretic peptide, HANP; human atrial natriuretic peptide, CSF; cerebrospinal fluid.

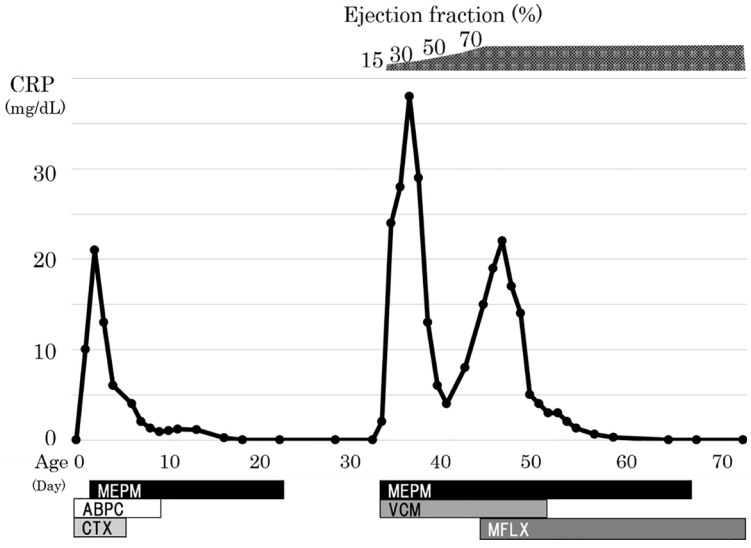

Fig. 1. Clinical, laboratory, and therapeutic course of two episodes of meningitis. CRP, C-reactive protein; MEPM, meropenem; ABPC, ampicillin; CTX, cefotaxime; VCM, vancomycin; MFLX, moxifloxacin.

showed no abnormality.

On Day 32 (10 days after discontinuation of MEPM), the patient suddenly became drowsy, with marked tachycardia (200–250 beats/min). Laboratory data revealed leukopenia and elevated serum CRP, creatinine kinase (MB-isozyme) and troponin-T levels. Notably, echocardiography revealed a dilated and severely hypokinetic left ventricle (ejection fraction, 15%), which was not observed during the first episode (Fig. 1). We initiated inotrope therapy, and the response was good. *E. coli* was again isolated from the blood and CSF. The patient received MEPM and vancomycin for 33 days, and moxifloxacin for 28 days. The patient was discharged at 10 months of age with a diffuse brain abnormality on MRI. Severe neurologic sequelae at discharge included neurodevelopmental delay and bilateral hearing impairment. The patient has suffered no recurrence of infection for more than 3 months and has regained normal left ventricular function without medication.

Susceptibility testing of the two isolates at 0 and 32 days of age revealed identical drug-resistant phenotypes. The two isolates also shared identical genetic sequences (O11;H18 serotype, sequence type 69), and drug-resistant genotype (*aac(3)-IId*, *strA/B*, *aph(3)-Ia*, *aadA5*, $bla_{\text{CMY-2}}$, $bla_{\text{TEM-1}}$, *mph(A)*, *tetB*, and *dfrA17*).

We next examined the conditions underlying the recurrent meningitis. No anatomic defects were detected by cranial and spinal MRI. Screening tests for primary immunodeficiency (serum immunoglobulin and complement levels, lymphocyte surface markers, lymphocyte proliferative response to phytohemagglutinin, and neutrophil function tests) were all normal range for his age. Trough concentrations of MEPM in the CSF were 7.3, 15.0, and 2.6 μg/ml on Days 42, 51, and 63, respectively.

Viral culture of the stool, urine, and throat swab was obtained on Day 32 for a differential diagnosis of sudden cardiac dysfunction. The stool culture yielded echovirus 18. A serological neutralization test for echovirus 18 was negative on Day 33, but persistently positive from 2 weeks later, suggesting that echovirus 18 was the pathogen responsible for the patient's recurrent illness.

Discussion

We present a rare case of recurrent *E. coli* meningitis in a preterm infant. The strains harbored several drug-resistant genes. Among them, $bla_{\text{CMY-2}}$ was of greatest importance because this AmpC β-lactamase confers resistance to penicillins, cephamycins, and third-generation cephalosporins [2], which are the first-line treatment in neonates with invasive bacterial infections. However, the isolates were susceptible to carbapenems, and trough CSF concentrations of MEPM were adequate and above the minimum inhibitory concentrations. The patient showed a good clinical response to MEPM, with no signs of chronic parameningeal infection detected by cranial MRI after discontinuation of the first course of treatment.

We thoroughly investigated the specific risk factors for recurrence, but identified no anatomical abnormalities or immunodeficiency in the patient. Nonetheless, there are two possible reasons for recurrence: one is related to virulence factors expressed by *E.coli* stains and the other is co-infection of echovirus. Sequence type 69 strain is an extra-intestinal pathogenic *E.coli* (ExPEC). Most ExPEC express multiple virulence factors, which could allow the microbes to survive in the patient's CSF [3] despite administration of the standard treatment during the first course. There is a possibility that the infection was not eradicated upon completion of the initial 21 day treatment.

Notably, serological assays and viral culture identified co-infection with echovirus 18. The presentation at the time of recurrence was fulminant, with severe cardiogenic shock due to myocarditis. Echovirus infections can cause myocarditis. We speculated that echovirus infection was not the sole co-infection, but might have contributed to recurrence of meningitis. Surveillance stool culture on Day 29 yielded Gram-negative bacilli; unfortunately, we were unable to determine whether this strain was identical to the isolates responsible for meningitis. Gastroenteritis or ischemia due to cardiogenic shock caused intestinal mucosal damage might be sufficient to allow bacterial translocation, leading to bacteremia and meningitis. Some case reports describe secondary bacteremia following viral infection [4] and suggest a similar pathogenesis. A recent study indicates that co-infection with enterovirus and *E. coli* is common in very young infants, and that existence of viral infection might go unnoticed [5]. Recurrence occurred during the in-patient course; none of the family members or the medical staff showed symptoms suggestive of viral infection. Thus, the route of the infection was not identified.

Here, we present a rare case of recurrent *E. coli* meningitis in a preterm infant, which may be due to co-infection with echovirus.

Conflict of interest statement

The authors have no conflicts of interest relevant to the content of this article.

Acknowledgement

We thank Dr. Kunihiko Morita and Dr. Kana Matsumoto (Doshisha Women's College of Liberal Arts) for help with measuring MEPM concentration.

References

[1] Edwards MS, Baker CJ. Bacterial infections in the neonate. In: Long SS, Pickering LK, Prober CG, editors. Principles and Practice of Pediatric Infectious Diseases. 4th ed.Philadelphia: Elsevier Saunders; 2012. p. 538–44.
[2] Yamasaki K, Komatsu M, Abe N, Fukuda S, Miyamoto Y, Higuchi T, et al. Laboratory surveillance for prospective plasmid-mediated AmpC beta-lactamases in the Kinki region of Japan. J Clin Microbiol 2010;48:3267–73.
[3] Miajlovic H, Aogain MM, Collins CJ, Rogers TR, Smith SG. Characterization of Escherichia coli bloodstream isolates associated with mortality. J Med Microbiol 2016;65:71–9.
[4] Gözmen S, Sükran Gözmen K, Apa H, Aktürk H, Sorguç Y, Bayram N, et al. Secondary bacteremia in rotavirus gastroenteritis. Pediatr Infect Dis J 2014;33:775–7.
[5] Calvo C, Gallardo P, Torija P, Bellón S, Méndez-Echeverría A, Del Rosal T, et al. Enterovirus neurological disease and bacterial coinfection in very young infants with fever. J Clin Virol 2016;85:37–9.