Case Report

Community-acquired CTX-M-15-type ESBL-producing *Escherichia coli* meningitis: a case report and literature review

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Abstract

In this report, a case of community-acquired acute bacterial meningitis (CA-ABM) caused by CTX-M-15-producing *Escherichia coli* in an elderly male patient was presented in the light of literature. Cultures of cerebrospinal fluid, blood, ear discharge, and stool samples yielded CTX-M-15-producing *E. coli in-vitro*, which was resistant to the extended-spectrum cephalosporins and ciprofloxacin and susceptible to imipenem, meropenem and amikacin. Meningitis was treated with parenteral meropenem plus parenteral and intraventricular amikacin administration. Since bacterial meningitis is a life-threatening infection, empiric antibiotic therapy with carbapenem can be started before the culture results are obtained, mainly in areas where the ESBL epidemiology is well known.

Key words: *Escherichia coli*; CTX-M-15; meningitis

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Introduction

Bacterial meningitis is a medical emergency which is associated with high mortality, neurological sequela, and community-acquired acute bacterial meningitis (CA-ABM) causing *Escherichia coli* is a rare entity. The most important prognostic factor is the appropriate choice of pathogen-specific antibacterial therapy [1,2]. For Gram-negative bacillary meningitis, current guidelines recommend the use of a third-generation cephalosporin guided by *in-vitro* susceptibility test results [3]. Extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli cause a significant therapeutic challenge since they hydrolyze all β-lactams except carbapenems and cephamycins. *E. coli* remains one of the main ESBL-producing microorganisms isolated worldwide. Among the ESBLs, the cefotaximases (CTX-M) constitute a rapidly growing cluster of enzymes, and CTX-M-producing *E. coli* has emerged and disseminated worldwide as an important cause of both nosocomial and community-acquired infections [4,5]. Recent studies from Turkey show that CTX-M-15 is the most prevalent ESBL among the CTX-M in *E. coli* strains [6-8]. Herein, we report a case of CA-ABM secondary to chronic otitis media and cerebrospinal fluid (CSF) fistula caused by CTX-M-15 type ESBL-producing *E. coli* in an elderly male patient. A review of the English-language medical literature is emphasized on the ESBL-type, origin, patient characteristics, treatment, and outcome of *E. coli* meningitis.

Case report

An 84-year-old man was admitted to the emergency department with a one-day history of aphasia and confusion. His relatives reported that he had a history of chronic intermittent purulent right ear discharge over the course of a few months, for which he refused medical care. They also noted that he had had complaints of fever, chills, vomiting, and headaches prior to the development of aphasia and confusion. His past medical history revealed a right tympanoplasty operation for chronic otitis media three years ago. Before his admission, he had also received oral ciprofloxacin (1 gram daily in two divided doses) treatment for three weeks for chronic prostatitis and but he had stopped taking this medication five days previously. On physical examination, he was

unconscious with a body temperature of 37.8°C, pulse rate was regular with a rate of 90 beats per minute, blood pressure was 110/60 mmHg, and respiratory rate was 20 breaths per minute. The respiratory system, cardiovascular system, and abdomen were normal. Otoscopic examination showed purulent discharge, tympanic membrane perforation, and a moderate hyperemia in the right ear. Neurological examination showed nuchal rigidity and ptosis of the left eyelid.

Laboratory analysis revealed a white blood cell (WBC) count of 13.700/mm^3, a serum C-reactive protein (CRP) level of 201 mg/l, and an erythrocyte sedimentation rate of 127 mm/h. Lumbar puncture was immediately performed and analysis of the CSF showed 2.200 leukocytes/mm^3 (90% polymorph nuclear), increased protein (495 mg/dl), decreased glucose (4 mg/dl with a concurrent blood glucose level of 121 mg/dl), and Gram-negative rods. A Gram stain from the ear discharge revealed the presence of multiple leukocytes and Gram-negative rods. Empiric intravenous ceftriaxone treatment (4 gr/day in 2 divided doses) was started immediately after the cultures were performed. An enhanced computerized tomography (CT) scan of the brain demonstrated ventricular dilatation (communicating hydrocephalus) and a defect in the right mastoid bone (secondary to previous ear surgery) as a cause of CSF leakage and acute purulent meningitis. The patient underwent external ventricular drainage for the management of CSF leakage from the ear.

However, his clinical situation worsened on the second day of admission and ceftriaxone treatment was switched to intravenous meropenem (3 gr per day in three divided doses) for the possibility of resistance. On the third day, cultures from CSF and ear discharge samples grew ESBL-producing *E. coli* which was resistant to extended-spectrum cephalosporins (ESCs) and ciprofloxacin, but susceptible to amikacin and carbapenem (imipenem and meropenem) antibiotics (Table 1). Throat culture was evaluated as normal flora. Stool culture was performed for the possible source of meningitis, and a fecal carriage of ESBL-producing *E. coli* yielded an ESBL-producing *E. coli* strain having the same antimicrobial susceptibility pattern with the previous *E. coli* strains.

CSF examination, which was repeated on the third day of meropenem treatment, showed minimal improvement in CSF findings: 1.800 leucocytes/mm^3, a protein level of 150 mg/dL, and a glucose level of 9 mg/dL . Therefore, intravenous and intraventricular amikacin 1.5 gr per day in three divided doses and 30 mg per day were added to the regimen, respectively. CSF examination on the sixth day of meropenem and the third day of intraventricular amikacin treatment revealed 2.700 leucocytes/mm^3, protein level of 390 mg/dL and glucose level of 4 mg/dL. Cultures from the second CSF sample and blood grew ESBL-producing *E. coli* with the same antimicrobial susceptibility pattern as in the previous *E. coli* isolates, suggesting the same microorganism. All four *E. coli* strains were sent to the Kocaeli University, Microbiology Lab, Turkey, for the determination of ESBL-type. On the seventh day of admission, revision mastoidectomy operation was performed due to the persistent right ear discharge. The stool culture on the 14th day of meropenem treatment and the CSF culture on the 17th day of the antibiotic regimen were still positive for the presence of ESBL-producing *E. coli*. CSF examination on the 28th and the 30th days of meropenem treatment showed 200 and 48 leucocytes/mm^3, 120 and 45 mg/dL of protein levels and 41 and 54 mg/dL of glucose levels, respectively. CSF culture was negative for the first time on the 28th day of meropenem treatment; therefore, antibiotics were discontinued on the 30th day. The results of three sequential CSF cultures with two-day intervals were negative and the patient's condition was stable after 30 days in the ICU.

Methodology

Sampling, identification procedure of microorganisms and antimicrobial tests

Blood samples were inoculated into blood culture bottles (BD BACTEC plus Aerobic/F, Shannon, County Clare, Ireland). CSF and ear discharge samples were inoculated onto sheep blood agar, chocolate agar, and EMB agar plates. One droplet of the positive growth blood cultures (BD BACTEC 9240 Blood Culture System, Franklin Lakes, NJ, USA) was placed on sheep blood agar, chocolate blood agar, and EMB agar plates and pricked by a sterile needle. Sheep and chocolate blood agar plates were incubated in microaerobic conditions and EMB agar plates were incubated in aerobic conditions at 37ºC for 24 to 48 hours. Stool samples were inoculated onto an EMB agar plate containing 2 µg/mL of cefotaxime for selection of ESBL-producing strain. The isolates were identified to the species level and tested for susceptibility to various antimicrobial agents and for ESBL-production by Phoenix 100 (BD Diagnostic Instrument Systems, Towson, Md.) automatic system using the manufacturer's Gram-negative Breakpoint/ID Panels (BD Phoenix NMIC/ID-82).

Table 1. Antimicrobial susceptibility pattern of *Escherichia coli* isolated from the cerebrospinal fluid (CSF)

Antibiotic	**MIC** (μg/mL)	**Interpretation**
Amikacin	≤ 8	S
Amoxicillin/clavulanate	16/8	R
Ampicillin	> 16	R
Aztreonam	> 16	R
Cefazolin	> 16	R
Cefepime	> 16	R
Cefotaxime	> 32	R
Cefoxitin	≤ 4	S
Ceftazidime	> 16	R
Chloramphenicol	8	S
Ciprofloxacin	> 2	R
Gentamicin	> 8	R
Imipenem	≤ 1	S
Levofloxacin	> 4	R
Meropenem	≤ 1	S
Piperacillin	*> 64*	*R*
Piperacillin/tazobactam	16/4	S
Tetracycline	> 8	R
Trimethoprim/sulfamethoxazol1/19	0.5/9.5	S

MIC = minimum inhibitory concentration, S = susceptible, R = resistant

ESBL typing and sequence analysis of E. coli strains

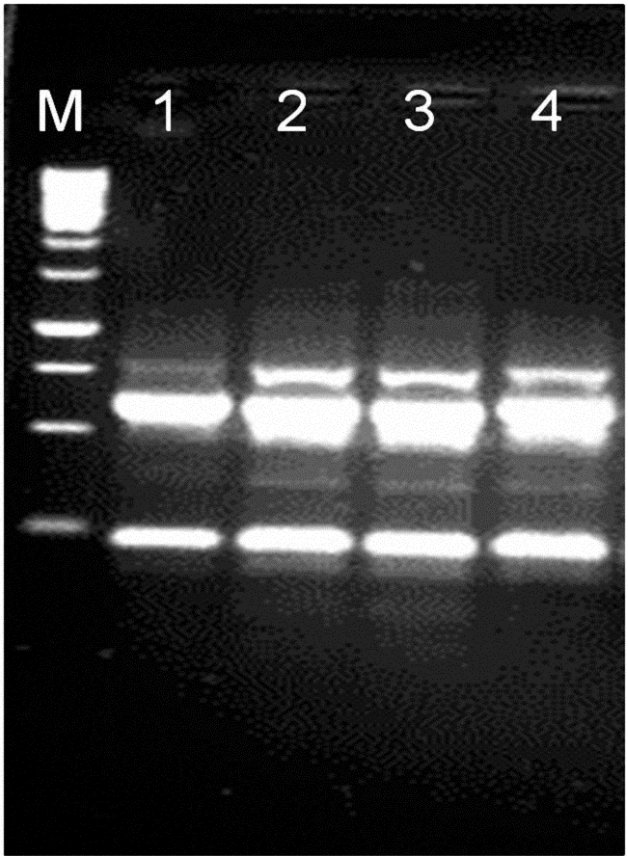
Fragment length patterns obtained by Random Amplified DNA (RAPD) PCR of the four *E. coli* were identical, indicating the clonality among isolates [9] (Figure 1). Isoelectric focusing revealed the existence of a single beta-lactamase at (approx.) pI 8.5 while PCR and sequencing of an 876 bp fragment amplified by CTX-M primers (CTXoF5'ATG GTT AAA AAA TCA CTG CGC-3' & CTXoR5'TTA CAA ACC GTC GGT GAC GAT-3') confirmed the existence of $bla_{\text{CTX-M-15}}$ in all four isolates. Sequencing was performed on both strands by the aid of four primers; two primers were used for amplification and the other two were inner primers (5'-ATG TGC AGC ACC AGT AAA GT-3' and reverse primer: 5' CCC CCA CAA CCC AGG AAG CA-3'), as described elsewhere [10].

Discussion

A review of the current English-language medical literature revealed a total of 8 cases of ESBL-producing *E. coli* meningitis, including the present case [1,11-15] (Table 2). Four were nosocomial and the other three were CA-ABM cases. Molecular typing and the ESBL-type of *E. coli* strains were determined in six strains and four of them were CTX-M-15, one was CTX-M-2, and the other was TEM-52-producing *E. coli*. It has been reported that all the nosocomial *E. coli* meningitis cases occurred during the outbreaks in infants in neonatal wards [1,11,12,14]. Two CA-ABM caused by ESBL-producing *E. coli* occurred in adults (Table 2).

In the presented case, PCR and sequence analysis showed that the intestinal colonization of the ESBL-producing *E. coli* was the source of bacterial meningitis. We postulate that the route of CSF infection in this case was due to the CSF fistula followed by ear contamination via the patient's hands. There is a relationship between the fecal carriage of ESBL-producing microorganisms and urinary tract infection in the community. The prevalence of fecal carriage of ESBL-producing microorganisms in these patients is reported to be 67.9% [16]. While hospitalization is a risk factor for intestinal colonization of ESBL-producing microorganisms, it is not a risk factor for CTX-M-type ESBL-producing *E. coli* colonization, suggesting that the colonization is acquired in the community. Detection of CTX-M-producing *E. coli* strains in the samples from livestock shows that animals might act as an important reservoir [4]. However, these strains may colonize in the gastrointestinal system of infants and may also cause an outbreak in the newborn units [1,11,12]. It has been previously demonstrated that fluoroquinolone use, advanced age, and severe underlying disease are

Figure 1. RAPD-PCR for *Escherichia coli* isolates



M, DNA marker (1 kb); ESBL strains from ear discharge (lane 1); blood (lane 2); CSF (lane 3); and stool (lane 4) of the patient

independent risk factors for the acquisition of ESBL-producing isolates in the community setting, particularly CTX-M-type enzymes [7]. Our patient had all of these risk factors. Despite a 14-day course of intravenous meropenem and amikacin treatment, persistent fecal colonization of the ESBL-producing *E. coli* still continued and we decided that potent parenteral antibiotics did not have any effects on the fecal colonization of such resistant bacteria. A clinical study demonstrated that parenteral meropenem, despite being successful in treating the systemic illness, failed to protect the digestive tract from colonization of ESBL-producing *K. pneumoniae* [17].

The main risk factors for CA-ABM with *E. coli* are alcoholism, cirrhosis, malignancies, diabetes, and immunosuppressive therapy. Nosocomial *E. coli* meningitis occurs frequently after neurosurgery and it is usually associated with multi-drug resistant strains [15]. Our patient had a CSF fistula secondary to a right tympanoplasty operation three years ago. The literature review reveals clear data regarding the co-existing factors in four of the seven ESBL-producing *E. coli* meningitis cases; very low birth weight infants in two cases, infected cephalhematoma in one case, and alcoholism and aortic mycotic aneurisms in one case. The neonatal age is considered to be a significant risk factor for Gram-negative bacillary meningitis [18]. It has been observed that all the nosocomial ESBL-producing *E. coli* meningitis cases were within the neonatal age accordingly (Table 2).

Current therapy of Gram-negative bacillary meningitis is third-generation cephalosporin and gentamicin may be added to the therapeutic regimen if the causative agent is susceptible. Cefepime, meropenem, aztreonam, fluoroquinolone, and trimethoprim-sulfamethoxazole are the second-line antibiotics [3]. Fluoroquinolones are widely added to the therapeutic regimen because of their excellent CSF penetration and bactericidal activity in the neonatal period. However, resistance is frequently found in CTX-M-15-positive isolates, as seen in our *E. coli* isolates [1,8]. Nevertheless, meropenem, was given to the patient one day later and intraventricular amikacin

Table 2. Previous reports of meningitis in the English literature caused by extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli*

Authors [Ref. no.]	Year	Country	Age	Origin of meningitis	Predisposing factors	ESBL-type	Antibiotic treatment	Outcome
Ramdani-Bouguessa N, *et al.* [11]	2006	Algeria	Child Child	Nosocomial Community	No information No information	CTX-M-15 CTX-M-15	No information No information	Cured Cured
Boyer-Mariotte S, *et al.* [1]	2008	France	Child	Nosocomial	Very low birth weight infant	CTX-M-15	No specific treatment	Died
Moissenet D, *et al.* [12]	2010	France	Child	Nosocomial	Very low birth weight infant	TEM-52	Imipenem+ Gentamicin+ Ciprofloxacin	Cured
Andrade LN, *et al.* [13]	2010	Brazil	Child	No information	No information	CTX-M-2	No specific treatment	Died
Nakwan N, *et al.* [14]	2011	Thailand	Child	Nosocomial	Infected cephalhematoma	Not determined	Meropenem	Cured
Weyrich P, *et al.* [15]	2012	France	Adult	Community	Alcoholism, Aortic mycotic aneurisms	Not determined	Meropenem+ Ciprofloxacin	Meningitis cured, died during an operation
Present case	2012	Turkey	Adult	Community	Chronic otitis media, Cranial surgery, Cerebrospinal fluid fistula	CTX-M-15	Meropenem+ Amikacin	Cured

was also added to the regimen five days later. Although any antimicrobial agents have been approved by the Food and Drug Administration (FDA) in the United States for intraventricular or intratechal use, amikacin and gentamicin are the most used aminoglycosides [19]. When faced with ESBL-producing microorganisms, delay in initiating an appropriate antibiotic is significantly associated with death. The literature review reveals that treatment data is available in six of the eight ESBL-producing *E. coli* meningitis cases and two of them were fatal because of the inefficiency of the empiric antibiotic therapy. Although the emergence of resistance during carbapenem therapy has been reported, a relatively high rate of clinical success with carbapenem is demonstrated in patients infected with ESBL-producers [4,20]. The literature review also revealed that half of the cases were treated with a carbapenem (Table 2). The mortality rate among patients infected with ESBL-producing *E. coli* is threefold greater than that of patients infected with non-ESBL strains [21]. The overall mortality rate in Gram-negative bacillary meningitis varied from 25% to 100% [18,22] and death occurred in three (38%) of eight ESBL-producing *E. coli* meningitis cases (Table 2).

Conclusion

Physicians should be aware of the presence of ESBL production when they encounter a Gram-negative bacterium associated CA-ABM case, especially when there is a history of prior antibiotic use. Since bacterial meningitis is a life-threatening infection, empiric antibiotic therapy with carbapenem can be started before the culture results are obtained, mainly in areas where the ESBL epidemiology is well known.

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