doi: 10.5262/tndt.2018.2866

Catheter-Related Bacteremia due to *Enterobacter ludwigii* in a Hemodialysis Patient: First Report in the Literature

Hemodiyaliz Hastasında Kateter ile İlişkili Enterobacter ludwigii Bakteriyemisi: Tıbbi Literatürde İlk Bildirim

ABSTRACT

The *Enterobacter cloacae* complex, a member of the genus *Enterobacter*, consists of a group of bacteria that are responsible for serious infections in human beings. A recently identified member of the group, *Enterobacter ludwigii sp*, is an emerging source of clinically important infections, but, up until now, there has been no report of catheter related bacteremia due to *Enterobacter ludwigii sp*. in hemodialysis patients. We report a hemodialysis patient with catheter related bacteremia due to *Enterobacter ludwigii sp*. whose infection improved only partially by antibiotics that were expected to be fully effective, based on antibiotic susceptibility testing; the infection could be cured only after removal of the catheter.

KEY WORDS: Enterobacter ludwigii, Hemodialysis, Catheter, Bacteremia

ÖZ

Enterobacter cinsi üyesi olan *Enterobacter cloacae* kompleksi, insanda ciddi enfeksiyonlardan sorumlu bir grup bakteri içerir. Grubun yakın zamanda tanımlanan, *Enterobacter ludwigii* türlerinin klinik olarak önemli enfeksiyonlara neden olduğu bildirilmektedir; fakat şimdiye kadar, hemodiyaliz hastalarında, kateter ile ilişkili *E ludwigii* bakteriyemisi bildirilmemiştir. Kateter ilişkili *E ludwigii* bakteriyemisi olan hemodiyaliz hastası, in-vitro antibiyotik duyarlılık özelliklerine göre seçilen antibiyotik tedavisine kısmi yanıt verdi; bakteri eradikasyonu, antibiyoterapi ile birlikte kateter çekilmesi sayesinde sağlanabildi.

ANAHTAR SÖZCÜKLER: Enterobacter ludwigii, Hemodiyaliz, Kateter, Bakteriyemi

Süleyman KÖZ[1]
Esin OĞUZ[2]
Meryem TİMUÇİN[1]
Seyit Ali BÜYÜKTUNA[3]
Mustafa Zahir BAKICI[4]
Ferhan CANDAN[1]
Mansur KAYATAŞ[1]

1 Cumhuriyet University, Faculty of Medicine, Department of Nephrology, Sivas, Turkey
2 Cumhuriyet University, Faculty of Medicine, Department of Internal Medicine, Sivas, Turkey
3 Cumhuriyet University, Faculty of Medicine, Department of Infectious Diseases, Sivas, Turkey
4 Cumhuriyet University, Faculty of Medicine, Department of Clinical Microbiology, Sivas, Turkey

INTRODUCTION

Enterobacter ludwigii sp (*E. ludwigii*) is a fermentative, motile gram negative bacillus with catalase positive, oxidase and DNAase negative properties. Its characteristic features were identified recently and it is considered a member of the *E. Cloacae* complex that belongs to genus *Enterobacter*. The distinctive feature of *E. ludwigii* is its ability to grow on myo-inositol and 3-0-methyl-D-glucopyranose media. It has been isolated from stool, urine, venous lines and bronchoalveolar lavage fluid, and all strains in the original description were shown to be susceptible to gentamicin, meropenem and trimethoprim-sulphamethoxazole and ciprofloxacin (1). To the best of our knowledge, there is no report of hemodialysis catheter related infection with *E. ludwigii*. Herein, we present a case of catheter related bacteremia caused by *E. ludwigii* in a hemodialysis patient.

CASE REPORT

A 73-year-old male patient, who had been on a thrice-weekly hemodialysis schedule due to end stage kidney disease of unknown etiology for three years, experienced dyspnea, nausea, vomiting, mental confusion and shaking chills during the dialysis session. The history of the patient was negative for abdominal symptoms, including diarrhea. The patient had a cuffed double lumen tunneled dialysis catheter; there was no hyperemia or purulent discharge at the catheter exit site and the

Received : 05.06.2017
Accepted : 16.11.2017

Correspondence Address:
Esin OĞUZ
Cumhuriyet Üniversitesi Tıp Fakültesi,
İç Hastalıkları Anabilim Dalı,
Sivas, Turkey
Phone : +90 506 626 06 72
E-mail : esinoguz_88@hotmail.com

tunnel tract was also normal. His medications were calcium acetate tablet, multivitamin preparation tablets and budesonide inhaler.

His fever was 38.7 °C, heart rate 123/min and blood pressure 162/97 mm Hg. Blood oxygen saturation was 92% by pulse oximetry, creatinine 7.3 mg/dl, blood urea nitrogen (BUN) 36 mg/dl, alanine aminotransferase (ALT) 10 U/l, and aspartate aminotransferase (AST) 16 U/l. Other clinical and laboratory data of the patient are presented in Table I. Our preliminary diagnosis was catheter related bacteremia and vancomycin 1 g iv (every three days) plus piperacilline/tazobactam 2.25 gr iv (thrice a day) were started empirically.

All of the prior attempts for fistula creation had failed without maturation and the cuffed tunneled catheter was therefore a mandatory option for the patient. The last catheter had been inserted approximately 17 months earlier, and two more catheter related bacteremia episodes were recorded prior to this episode, both of which were treated with antibiotics without catheter removal. Blood cultures had grown *S. aureus* in one of these episodes; no other growth was noted.

Initial blood cultures of the patient grew *E. Ludwiggii,* and piperacillin/tazobactam treatment was continued as the susceptibility pattern dictated. Vancomycin treatment was suspended upon the results of blood cultures. In total, blood and /or catheter cultures grew *E. Ludwigii* on five different days. Antimicrobial susceptibilities of all isolates were identical (Table I).

The patient had a partial clinical response to piperacillin/tazobactam treatment, and it was continued until day 18. Although the frequency decreased, fever spikes that were higher than 38.3 °C were observed until day four. On day 18, the catheter was removed due to failure to eradicate *E. Ludwigii* infection; thereafter the patient further improved clinically, and cultures grew no *E. Ludwigii*. A thorough clinical examination, echocardiography, abdominal ultrasonography, and abdominal and thoracic computerized tomography were done to investigate the possible foci of the infection other than the catheter; none of the additional investigation could reveal a focus of additional infection. A temporary non-cuffed double lumen hemodialysis catheter was inserted one day after the removal of the infected catheter, which was replaced with a cuffed tunneled one five days later.

Piperacillin/tazobactam treatment was continued for 10 more days after removal of the catheter.

Laboratory methods for growing and isolation of the microorganism were as follows: Blood samples were inoculated into aerobic culture media (BD Bactec culture media) and incubated at 35±2°C in full automatic blood culture automate (BD Bactec FX, Maryland USA), for five days. Growth signals were received on the second day of incubation (for the cultures at the presentation). Then blood cultures were sub-cultured in to 5% sheep blood agar and EMB media, and incubated at 35±2°C overnight; identification of the recovered Gram (-) bacteria was performed in the Bruker Maldi-TOF MS (Bruker, microflex model, Bremen, Germany) device automatically. Antibiotic

Table I: Selected clinical, microbiological and laboratory data of the patient.

Date	Blood Culture		Fever (highest value in 24-hour period, °C)	WBC (per mm^3)	CRP (mg/l)	Procalcitonin (ng/ml)
	Blood Drawn from Peripheral Vein	Blood Drawn from Hemodialysis Catheter				
At presentation	*E. ludwigii*	*E. ludwigii*	38.7	6450	82	23.8
Four days after presentation	No growth	*E. ludwigii*	38.4	12120	80	55
Eleven days after presentation	*E. ludwigii*	No growth	37.5	13070	92	7.08
Eighteen days after presentation	*E. ludwigii*	*E. ludwigii*	37	6460	106	2.85
Five days after removal of the infected catheter	No growth	No Growth	36.9	7460	132	1.94
Susceptibility pattern of the *E. ludwigii* (MIC, micg/l)	Amikacin ≤ 4 Amoxicillin/Clavulanate ≥ >32/2 Ampicillin>8 Ceftazidime <0.5 Ceftriaxone <0.5			Ciprofloxacin < 0.125 Gentamicin < 1 Piperacillin/Tazobactam < 4/4 Trimethoprim/Sulfamethoxazol <1/19		

susceptibility was tested in BD Phoenix 100 (Maryland, USA), and the results are shown in Table I. Antimicrobial sensitivity tests were performed in accordance with standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2), and the sensitivity patterns of the all isolates were identical. Culture of the catheter tip did not result in microbial growth.

DISCUSSION

Twenty-two species are classified under the *Enterobacter* genus. Six of these species, *E. cloacae*, *asburiae*, *hormaechei*, *kobei*, *ludwigii* and *nimipressuralis* are combined together to form a group named the *E. cloacae* complex. These six species have a common DNA sequence of around 60% similarity (3). Members of Enterobacteriaceae are responsible from many serious human infections, including catheter related ones. Catheter related bacteremia in hemodialysis patients is a serious infection that may result in sequelae, and might follow a fatal course. Although Enterobacteriaceae are well known etiologic agents in catheter related bacteremia, there is not enough data about *E. Ludwigii* (4). There may be some species-specific clinical differences between infections caused by bacteria of the Enterobacteriaceae family, so precise identification of the bacteria may have clinical importance.

From the infectious disease point of view, the most effective and direct way to treat catheter related bacteremia is removal of the catheter immediately upon the diagnosis of bacteremia. However, these patients need to be dialyzed, and some may have severe access problems, as was in our case. It is suggested that the decision of catheter removal should be individualized on basis of patient's clinical status. Catheter salvage can be attempted in the course of some gram negative bacteremia (5). Our policy is to remove non-cuffed hemodialysis catheters immediately but we initially try to treat the infection with antibiotics in cuffed tunneled catheters. If the infection does not improve with antibiotics, or fever persists beyond seven days, we remove the catheter, and insert a non-cuffed catheter one day after the removal of the previous catheter. If the infection is severe and the patient is unstable, we do not attempt catheter salvage at all. Intensity of fever in our patient decreased upon antibiotic treatment, and other vital signs followed a stable course. Because vascular access in our patient was very problematic, we tried to save the catheter with maximal effort. In any case, this patient is very exceptional, in that we never suggest such a long antibiotic trial in any patient.

Duration of antibiotic therapy in catheter related bacteremia differs according to the causative agent; C-reactive protein (CRP) and procalcitonin are two well-known acute phase reactants that are auxiliary in guiding the treatment. At the moment we stopped antibiotics, the CRP level was still high. Although CRP is also accepted as an indicator of bacterial infections, we relied more on clinical status and procalcitonin level of the patient. It is reported that procalcitonin is a reliable indicator of bacterial eradication (6).

Enterobacteriaceae are gram-negative bacilli that can be found in animals, plants and water (3). Their biofilm producing characteristics are also well documented (7). As far as we know, there is no documentation or characterization of biofilm of *E. ludwigii,* but there is data that they have a good capacity to adapt to the environment; some isolates can produce extrapolysaccharides that protect them from a radioactive environment (8). Although the isolates in our patient were susceptible to Piperacillin/Tazobactam, the clinical cure of the infection could not be attained until the removal of the catheter. It might indicate inadequate antimicrobial exposure of the bacteria embedded in the biofilm layer.

A nosocomial outbreak of *E. ludwigii* that was recovered from blood cultures of the pediatric patients treated in an intensive care unit has been reported recently. The susceptibility pattern of our and their isolates exhibits some differences; isolate in our case was susceptible to amikacin, ceftazidime, and gentamicin, whereas their isolates were not; isolates in both reports were susceptible to tazobactam/ piperacillin (9). Hoffmann et al reported that 20% of the isolates were resistant to tazobactam/ piperacillin (1). Carbapenem resistance is low among the *E. Cloacae* complex, although it is being reported with increasing frequency (3,10). Would the use of carbepenem in our patient made a difference in terms of clinical response, or salvage of the catheter? Our laboratory did not report susceptibility of isolates to carbapenems. We speculate that the problem in our patient might be due to inaccessibility of the bacteria within the biofilm on the catheter. We therefore suppose that it would have made no difference, since it could not have penetrated into the putative biofilm either. Additionally, *E. cloacea* complex species might produce class A carbapenemases that result in carbepenem resistance; tazobactam has ability to inhibit these carbepenems (3). Compared to carbapenems, the tazobactam-piperacilline combination might therefore be an even more reasonable choice of treating some *E. cloacea* complex infections. The value of preventive measures for catheter related infections in hemodialysis units is undisputed. Most of the catheter related infections are related to inadequate treatment of the catheters both by staff and by patients. In our hemodialysis center, we follow the guidelines of the Centers for Disease Control (CDC) for dialysis catheters (11). We do not use antibiotic ointments routinely for catheter exit-site care and we use iodinated antiseptics or chlorhexidine instead. Our patient was treated with multiple courses of antibiotics that might increase the risk of the infection. It has been shown that exit-site care with topical antibiotics may decrease both local and systemic catheter related infections (5). We might speculate that the use of antibiotic ointment could have prevented the catheter related infection in our patient.

CONCLUSION

The clinical course of our patient shows that *E. ludwigii* can cause serious catheter related infections in hemodialysis patients and in some cases the infection can be eradicated only by catheter removal. We suggest strictly following infection control rules to decrease catheter related infection rates at hemodialysis centers.

Informed consent was received from the patient. The authors declare that they have no conflict of interest.

REFERENCES

1. Hoffmann H, Stindl S, Stumpf A, Mehlen A, Monget D, Heesemann J, Schleifer KH, Roggenkamp A: Description of enterobacter ludwigii sp. nov., a novel Enterobacter species of clinical relevance. Syst Appl Microbiol 2005;28:206-212
2. EUCAST:The European Committee on Antimicrobial Susceptibility Testing.MIC distributions and ECOFFs. 2017 Jan. http://www.eucast.org/mic_distributions_and_ecoffs
3. Mezzatesta ML, Gona F, Stefani S: Enterobacter cloacae complex: Clinical impact and emerging antibiotic resistance. Future Microbiol 2012;7:887-902
4. Landraud L, Brisse S: Enterobacteriaceae. Infectious Diseases. London:Mosby 2010; 1690-1703
5. Dixon BS, Dember LM: Vascular Access. In: Himmelfarb J, Sayegh MH (eds), Chronic Kidney Disease, Dialysis, and Transplantation. (3rd ed). Phyladelphia: Sounders-Elsevier, 2010. [İnternet yayını] [Atıf: 14.11.2017] Erişim: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781437709872000522
6. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B: Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: A randomized trial. Am J Respir Crit Care Med 2006;174:84-93
7. Donlan RM, Costerton JW: Biofilms, survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev 2002;15:167-193
8. Pau-Roblot C, Lequart-Pillon M, Apanga L, Pilard S, Courtois J, Pawlicki-Jullian N: Structural features and bioremediation activity of an exopolysaccharide produced by a strain of Enterobacter ludwigii isolated in the Chernobyl exclusion zone. Carbohydr Polym 2013;93:154-162
9. Flores-Carrero A, Labrador I, Paniz-Mondolfi A, Peaper DR, Towle D, Araque M: Nosocomial outbreak of extended-spectrum b-lactamase-producing Enterobacter ludwigii co-harbouring CTX-M-8, SHV-12 and TEM-15 in a neonatal intensive care unit in Venezuela. J Glob Antimicrob Resist 2016;7:114-118
10. Khajuria A, Praharaj AK, Grover N, Kumar M: First report of an Enterobacter ludwigii isolate coharboring NDM-1 and OXA-48 carbapenemases. Antimicrob Agents Chemother 2013;57:5189-5190
11. Committee. Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011. [İnternet yayını] [Atıf: 14.11.2017] Erişim: https://www.cdc.gov/hai/pdfs/bsi-guidelines-2011.pdf