CASE REPORT

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Multidrug-Resistant *Elizabethkingia anophelis*, A Rare Causative Agent of Bacteremia in a Hemodialysis Patient Hospitalized in the Intensive Care Unit: First Case in North Cyprus

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Abstract

Elizabethkingia spp. bacteria are found in living and non-living things. *Elizabethkingia meningoseptica (E. meningoseptica)* and *Elizabethkingia anophelis (E. anophelis)* are the leading species that can cause diseases in humans. Most of the infections (80-87.5%) caused by *E. anophelis* are hospital-acquired. This bacterium is generally identified as *E. meningoseptica* by automated systems. In this study, a case of bacteremia due to *E. anophelis* in a hemodialysis patient is presented. This patient is a 72 years old female who is hospitalized in the intensive care unit. She was referred to the Near East University Hospital from the state hospital with pneumonia. *E. anophelis* was isolated from the patient's blood culture by the VITEK-2 automated system. The isolated bacteria were stored at -80 ºC and detected as *E. anophelis* by matrix-assisted laser desorption ionization time of flight. Success was achieved by adding levofloxacin to the ongoing meropenem treatment in our patient. Although the transmission route of our case with multidrug resistance is not exactly known, it is assumed that the transmission originated from the hospital. In this regard, increasing control measures in hospitals, mainly in water systems, will prevent such infections and deaths. In addition, it is concluded that for treating infections caused by *Elizabethkingia*, the use of fluoroquinolones should be the first choice.

Keywords: *Elizabethkingia anophelis*, bacteremia, hemodialysis, rare, North Cyprus

INTRODUCTION

Bacteria in the genus *Elizabethkingia* spp. are Gram-negative, aerobic, pale, yellow pigmented, non-motile, non-glucose fermenting, and oxidase positive. They are ubiquitously distributed in nature, including water, soil, sediment, plants, fish, frogs, insects, and some animal digestive tracts. *Elizabethkingia meningoseptica*, *Elizabethkingia anophelis*, *Elizabethkingia miricola*, *Elizabethkingia bruuniana*, *Elizabethkingia ursingii*, and *Elizabethkingia occulta* are known species of bacteria. The leading species that cause diseases in humans are

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Elizabethkingia meningoseptica (*E. meningoseptica*) and *Elizabethkingia anophelis* (*E. anophelis*).[1,2]

E. anophelis is a newly discovered bacterium isolated from the gut of *Anopheles gambiae* mosquito.[3] It is reported as an opportunistic bacterial pathogen that causes bacteremia in immunocompromised elderly patients and newborns.[4] Moreover, this bacterium can cause meningitis, pneumonia, septic arthritis, osteomyelitis, endocarditis, conjunctivitis, and cholangitis.[1] Most of the infections caused by *E. anophelis* (80%-87.5) are hospital-acquired. These bacteria, which can colonize hospital environments, are resistant to applied decontamination processes. In addition, hospitals are considered to be reservoirs of these bacteria since they can contaminate water systems, solutions, and hospital equipment.[1,5]

In recent years, an increase in *E. anophelis* infections that threaten human life has been reported in clinics.[6] In society, *E. anophelis* infection in humans was first observed in 2012 at a hospital in Singapore, when *E. anophelis* was isolated from five patients with a nosocomial infection. In two of these patients, infection resulted in death due to sepsis.[7] According to the literature, several epidemics were seen in Hong Kong, Taiwan, and the United States in the following years.[5]

Routine phenotypic and biochemical tests often fail to distinguish *E. anophelis* from other bacteria. At the same time, this bacterium is usually defined as *E. meningoseptica* by automated systems.[5] Additionally, the multi drug resistance (MDR) of the bacterium and the lack of a standard antibiotic susceptibility profile make empirical treatment almost impossible.[4] The mortality rate in *E. anophelis* infections due to MDR is estimated to vary between 24% and 30%.[2]

Early and accurate determination of appropriate antibiotic susceptibility results is critical and crucial to reduce morbidity and mortality in patients infected with *E. anophelis*. In our study, a case of bacteremia due to *E. anophelis* in a hemodialysis patient hospitalized in an intensive care unit (ICU) is presented. In the literature, there is no reported case of *E. anophelis* that has been found in North Cyprus, and hence this infection is the first *Elizabethkingia* infection presented in our country.

CASE PRESENTATION

A 72-year-old Ukrainian woman residing in North Cyprus applied to the Near East University Hospital on April 01, 2022, as a referral from Dr. Burhan Nalbantoğlu State Hospital, Nicosia due to respiratory distress. The patient had no fever, was conscious and cooperative. She was also receiving meropenem (3x500 mg) treatment at the hospital she came to. The patient had chronic renal failure and was on regular hemodialysis. First, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) antigen and SARS-CoV-2 RNA polymerase chain reaction test (PCR) were performed on the patient, and she was hospitalized in the general ICU with negative results. Meanwhile, biochemical test were performed from the taken blood and the results were: uric acid (1.7 mg/dL), albumin (2.8 g/dL), amylase (15 U/L), lipase (<4 U/L), and calcium (8.2 mg/dL) were found to be low. In addition, creatinine (2.63 mg/dL), aspartate aminotransferase (AST) (52 U/L), procalcitonin (PCT) (12.26 ng/mL), and C-reactive protein (CRP) (28.63 mg/dL) elevations were noteworthy. In the complete blood count, hemoglobin (12.1 g/dL), and WBCs ($4.4x10^3$/µL) levels were found to be normal, but thrombocytopenia ($47x10^3$/µL) was detected in the patient.

Considering all these results and respiratory failure, thoracic computed tomography (CT) was performed on April 02, 2022. According to the CT results, massive pleural effusion in the right hemithorax and almost complete loss of aeration in the lower lobe of the right lung were observed. In addition, 14 mm thick pleural fluid was detected in the left hemithorax.

Samples for sputum and blood culture were taken from the patient on the day of hospitalization. The sputum sample was inoculated on blood agar and eosin methylene blue (EMB) agar and incubated for 24-48 hours at 35 ºC. Blood samples were taken from the patient's right and left arm at an interval of 15 min. The samples (8-10 mL) taken for blood culture were transferred to BD BACTEC Plus Aerobic/F bottles and loaded into the BACTEC 9120 (Becton, Dickinson and Company Sparks, USA) device. Two days later, when positive signals were received from the device, the blood sample was drawn with a sterile syringe from the blood culture bottles and inoculated on blood and EMB agars; the agars were incubated 35 °C for 24-48 hours. With the observation of growth in both sputum and blood cultures, suspensions were prepared from the colonies that grew in line with the manufacturer's VITEK-2 (BioMerieux, Inc. Durham, USA) compact automated system. In addition, smears were prepared from both colonies and stained with Gram-stain. Structures of *Candida* species were seen in the Gram-stain of colonies grown in sputum culture and *Candida albicans* was obtained as a result of VITEK-2. Gram-negative bacilli were observed in smear preparations made from colonies grown in both blood cultures. Upon this, bacteria identification (VITEK-2 GN ID card) and antibiotic susceptibility test (AST) (VITEK-2 AST-N326 card) were performed. AST was evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria. The result of *Elizabethkingia meningoseptica* was obtained by the automated system. According to the results of the antibiotic tests, only ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole (SXT) were susceptible. The AST results given by the VITEK-2 automated system of the bacteria are presented in Table 1. Considering the antibiogram, levofloxacin (1x500 mg) was added to the patient's ongoing meropenem (3x500 mg) treatment. Furthermore, 72 h later, a

Table 1. AST results of *Elizabethkingia anophelis* obtained from VITEK-2 automated system

Antibiotic	MIC (µg/mL)	Result
Piperacillin	64	I
Piperacillin/tazobactam	>=128	R
Ceftazidime	>=64	R
Cefepime	>=32	R
Aztreonam	>=64	R
Imipenem	>=16	R
Meropenem	>=16	R
Amikacin	>=64	R
Gentamicin	>=16	R
Netilmicin	>=32	R
Tobramycin	>=16	R
Ciprofloxacin	1	S
Levofloxacin	1	S
Tetracycline	8	I
Trimethoprim/sulfamethoxazole	40	S

MIC: Minimum inhibitory concentration; S: Sensitive; R: Resistant; I: Intermediate, AST: Aspartate aminotransferase.

decrease was observed in our patient's CRP and PCT levels (13.20 mg/dL and 6.18 ng/mL, respectively). At the end of seventh day, CRP and PCT values were observed as 8.33 mg/dL and 3.31 ng/mL respectively. Our patient had undergone dialysis twice within a week during her stay in the hospital. At the end of a week, the patient returned to the State Hospital again. After that, no information could be obtained from the patient.

E. meningoseptica strains isolated from blood cultures were stocked using bacteria stock tubes (OR-BAK, Ankara, Türkiye) and stored at -80 ºC. Since it is a rare bacterium, the sample was sent to Dokuz Eylül University under the appropriate conditions and the bacterium was detected as *E. anophelis* by matrix-assisted laser desorption ionization time of flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

An informed consent form was filled by the patient and her consent was obtained, which allowed us to present our case.

DISCUSSION

The case presented in this study is the first reported case of *E. anophelis* infection detected in Cyprus. Because the patient came to the Near East University Hospital as a referral from a state hospital, the source of the infection is not known exactly. Even though the predominance of this bacterium in the gut microbiota of *Anopheles gambiae* mosquitoes indicates that mosquitoes can be vectors for transmission, there is no clinical evidence to support this view.[2] However, considering that the patient is hospitalized in the ICU of the state hospital and regularly undergoes dialysis, it is possible to think that the infection originates either from the ICU or hemodialysis units. Recent studies suggest that hospital environments act as reservoirs for *Elizabethkingia* species. In fact, despite the control measures taken in hospitals, it has been proven that the bacterium continues to exist in the water resources of hospitals.[8,9] In a study by Kyritsi et al.[10], two different *Elizabethkingia* strains were detected in the water system of the same hospital, three months apart. In view of the data obtained from our study, it is concluded that this bacterium was transmitted to our patient from the hospital environment.

E. anophelis is the dominant strain of the septicemia-causing *Elizabethkingia* genus and is associated with fulminant complications such as acute pulmonary edema, congestive heart failure, septic shock, and death. *E. anophelis* infections should always be considered as clinically significant unless proven otherwise. In addition, there exist studies in the literature showing that automated systems such as VITEK-2 misidentify *E. anophelis* isolates as *E. meningoseptica*.[11] MALDI-TOF systems are extensively used for microbial identification in clinical microbiology laboratories. Unfortunately, systems that are most frequently used for microbial identification like VITEK-2 cannot distinguish *Elizabethkingia* species. VITEK-2 automated system can detect only *E. meningoseptica* with its reference database. The lack of species information in the reference databases prevents these platforms from correct recognition of the species of *Elizabethkingia*. Although MALDI-TOF systems with a large database can reliably identify *E. anophelis* and *E. meningoseptica*, these platforms cannot distinguish between the remaining species of the genus *Elizabethkingia*.[12] Moreover, according to the most recent studies, it is emphasized that MALDI-TOF systems are no longer able to accurately identify *Elizabethkingia* species and therefore 16S rRNA or full genome sequence analyzes are required for accurate identification.[13] The strain isolated in this study could not be performed using 16S rRNA or full genome sequence analysis, which can be a limitation of our study. However, showing that this strain exists in Cyprus contributes to clinicians, scientists, and the literature.

E. anophelis has an extensive antibiotic resistance profile, including most penicillins, cefalosporines, carbapenems, aminoglycosides, and macrolide antibiotics. Fluoroquinolones, SXT, and piperacillin/tazobactam are used as first-line therapy for *Elizabethkingia* infections, but resistance recently complicates treatment. Teng et al. draw attention to SXT resistance in *Elizabethkingia* species.[14] The combination treatment of vancomycin, piperacillin/tazobactam, and ciprofloxacin gave positive results in a newborn case with meningitis and septicemia determined by Baruah et al.[11] Nielsen et al.[13] isolated *E. anophelis* from a 76-year-old male patient and applied moxifloxacin and rifampicin treatment for two weeks, which resulted in success. Because they can cross the blood-brain barrier more easily, fluoroquinolones, especially ciprofloxacin, are a good choice for these infections.[11] In this study, levofloxacin was combined with meropenem treatment in our patient who presented with septicemia, and as a result, success was achieved.

In conclusion, although the transmission route of our case with multidrug resistance (Table 1) is not known for certain, it is thought that it was caused by the hospital. In this regard, increasing control measures in hospitals, mainly in water systems, will prevent such infections and deaths. For *Elizabethkingia* typing, if the facilities are sufficient, sequence analysis must be performed. Furthermore, it is concluded that the use of fluoroquinolones should be the first choice for treating infections caused by *Elizabethkingia*.

MAIN POINTS

- *Elizabethkingia anophelis* is a rare bacterium and was first isolated in North Cyprus.
- Since it is multiple drug-resistant bacterium, treatment options should be determined correctly.
- It is critical to detect and eliminate the source of contamination, especially in units where immunosuppressed patients are treated, such as intensive care and hemodialysis.

ETHICS

Informed Consent: An informed consent form was filled by the patient and her consent was obtained, which allowed us to present our case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ç., G.E., K.S., Concept: E.G., N.Ç., K.S., Design: E.G., K.S., Data Collection and/or Processing: E.G., U.H., Ö.A.Ö., Analysis and/or Interpretation: U.H., N.Ç., Ö.A.Ö., G.E., K.S., Literature Search: E.G., Writing: E.G.

DISCLOSURES

Conflict of Interest: The authors have no conflicts of interest to declare.

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REFERENCES

1. Nievas J, Ibanez ML, Allende L, Altclas J, Antezana G, Campos J, et al. Emergence of Elizabethkingia anophelis. First case of E. anophelis outbreak in a neonatal unit of a hospital in Argentina. Clinical Infection in Practice. 2022; 13: 100122.
2. Wang B, Cheng R, Feng Y, Guo Y, Kan Q, Qian A, et al. Elizabethkingia anophelis: An Important Emerging Cause of Neonatal Sepsis and Meningitis in China. Pediatr Infect Dis J. 2022; 41(5): e228-32.
3. Kämpfer P, Matthews H, Glaeser SP, Martin K, Lodders N, Faye I. Elizabethkingia anophelis sp. nov., isolated from the midgut of the mosquito Anopheles gambiae. Int J Syst Evol Microbiol. 2011; 61(Pt 11): 2670-5. Erratum in: Int J Syst Evol Microbiol. 2012; 62(Pt 4): 1016.
4. Sahoo RK, Sahoo S, Das A, Gaur M, Bhanjadeo D, Panda P, et al. A phylogenetic study of Elizabethkingia anophelis bloodstream isolates obtained from inpatients at a single medical center. Infect Control Hosp Epidemiol. 2019; 40(10): 1202-4.
5. Aydemir O, Sahin Ozozen E, Elmas B, Caha V. A Rare Infectious Agent: Elizabethkingia anophelis; Second Case Reported from Turkey. Konuralp Medical Journal. 2022; 14(1): 168-71.
6. Xu L, Peng B, He Y, Cui Y, Hu Q, Wu Y, et al. Isolation of Elizabethkingia anophelis From COVID-19 Swab Kits. Front Microbiol. 2022; 12: 799150.
7. Teo J, Tan SY, Tay M, Ding Y, Kjelleberg S, Givskov M, et al. First case of E anophelis outbreak in an intensive-care unit. Lancet. 2013; 382(9895): 855-6.
8. Breurec S, Criscuolo A, Diancourt L, Rendueles O, Vandenbogaert M, Passet V, et al. Genomic epidemiology and global diversity of the emerging bacterial pathogen Elizabethkingia anophelis. Sci Rep. 2016; 6: 30379.
9. Moore LS, Owens DS, Jepson A, Turton JF, Ashworth S, Donaldson H, Holmes AH. Waterborne Elizabethkingia meningoseptica in Adult Critical Care. Emerg Infect Dis. 2016; 22(1): 9-17.
10. Kyritsi MA, Mouchtouri VA, Pournaras S, Hadjichristodoulou C. First reported isolation of an emerging opportunistic pathogen (Elizabethkingia anophelis) from hospital water systems in Greece. J Water Health. 2018; 16(1): 164-70.
11. Baruah FK, Borkakoty B, Ahmed A, Bora P. Neonatal Meningitis and Septicemia Caused by Multidrug-Resistant Elizabethkingia anophelis Identified by 16s Ribosomal RNA: An Emerging Threat. J Glob Infect Dis. 2020; 12(4): 225-7.
12. Lin JN, Lai CH, Yang CH, Huang YH. Elizabethkingia Infections in Humans: From Genomics to Clinics. Microorganisms. 2019; 7(9): 295.
13. Nielsen HL, Tarpgaard IH, Fuglsang-Damgaard D, Thomsen PK, Brisse S, Dalager-Pedersen M. Rare Elizabethkingia anophelis meningitis case in a Danish male. JMM Case Rep. 2018; 5(8): e005163.
14. Teng LC, Wang JM, Lu HY, Mao YC, Lai KL, Tseng CH, et al. Elizabethkingia Intra-Abdominal Infection and Related Trimethoprim-Sulfamethoxazole Resistance: A Clinical-Genomic Study. Antibiotics (Basel). 2021; 10(2): 173.