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Pneumonia due to *Enterobacter cancerogenus* infection

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Abstract *Enterobacter cancerogenus* (formerly known as CDC Enteric Group 19; synonym with *Enterobacter taylorae*) has rarely been associated with human infections, and little is known regarding the epidemiology and clinical significance of this organism. We describe a community-acquired pneumonia case in a 44-year-old female due to *E. cancerogenus*. Identification and antimicrobial susceptibility of the microorganism was performed by the automatized VITEK 2 Compact system (bioMerieux, France). The clinical case suggests that *E. cancerogenus* is a potentially pathogenic microorganism in determined circumstances; underlying diseases such as bronchial asthma, empiric antibiotic treatment, wounds, diagnostic, or therapeutic instruments.

In this report, we describe a case of community-acquired pneumonia in a 44-year-old female due to *Enterobacter cancerogenus* and clinical-microbiological management of the patient was evaluated. Physical examination, X-ray imaging, and biochemical analysis (neutrophilia, increase in erythrocyte sedimentation rate and CRP) were in concordance with pneumonia. *E. cancerogenus* was identified from sputum sample. Empiric therapy with cefuroxime axetil and clarithromycin was begun but any signs of healing was not observed until we switched off to the new antibiotic regimen consisting of levofloxacin (500 mg IV once daily) chosen on the basis of the susceptibility tests. Patient's clinical condition was gradually improved within the following 48 h. Follow-up cultures, radiological, and blood analysis confirmed the patient's healing with complete cure.

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Case report

A 44-year-old female was admitted to the Pulmonology Department of Ahi Evran University Research and Teaching Hospital, Kirsehir, Turkey, with the symptoms of productive cough, chest tightness, wheezing, shortness of breath, malaise, fever (38.9 °C), and back pain. In the previous week before admission, she noted an influenza-like illness. On physical examination, chest auscultation revealed inspiratory crackles over the lower lung fields. The chest X-ray showed bilateral dense alveolo-interstitial infiltrates especially in the lower lobes. The patient had a history of medication with inhaled salbutamol and montelukast in addition to inhaled corticosteroid for 6 years.

At the time of admission, acute phase reactants, total cell count, serum electrolyte levels, sputum culture, urine culture, and two sets of blood cultures were send to the laboratory. Platelet count was normal (363,000 μL) but increase in white blood cell count (12.6×10^3 μL) (83.9 % neutrophiles and 8.7 % lymphocytes) and slightly low levels of lymphocytopenia (1.1×10^3 μL) was detected. RBC (4.51×10^6 mL), hematocrit (37.9 %), and hemoglobin (12.9 g/100 mL) levels were below normal range. Serum erythrocyte sedimentation rate was high; 35 mm/30 s and 97 mm/min, and CRP was 8.0 mg/100 mL. Electrolyte levels and other laboratory parameters were in the normal range. Urine analysis was unremarkable, with urine and blood cultures being sterile. Empirical therapy with cefuroxime axetil per oral (2×500 mg/day) and clarithromycin (2×500 mg/day) begun. Gram-staining smear of the sputum sample

was evaluated for the presence of epithelial cells, polymorphonuclear leukocytes, and bacterial types. High number of gram-negative rod and gram-positive cocci were observed Bartlett's grading system (Winn et al. 2006) was used for quantification of the cell contents of the sputum and the final score of the sample was 1, with the observed number of squamous epithelial cells was <25 and leukocyte number was between 10 and 25 per low power field (LPF), indicating the active inflammation and the necessity for further analysis. Sputum specimen was inoculated onto 5 % sheep blood agar, eosin-methylene blue agar (EMB), and chocolate agar and incubated at 37 °C. After an overnight incubation, smooth type colony, lactose-positive in pure culture was observed on EMB agar but three types of colonies were detected on sheep blood agar and chocolate agar plates representing mostly gram-positive bacteria and less common gram-negative bacteria. Further tests were performed from subculture of EMB agar to blood agar. The strain was oxidase-negative and catalase-positive. Positive test results were obtained for nitrate reduction, urea hydrolysis, and motility. The strain was identified as *E. cancerogenus* by VITEK-2 Compact automated system (bioMerieux, France). Antimicrobial susceptibilities of the strain were evaluated by VITEK-2 Compact automated system and Kirby-Bauer disk diffusion test method according to the Clinical Laboratory Standard Institute (CLSI) guidelines (CLSI 2011). The sensitivity of the isolate to the third-generation cephalosporins, ceftriaxone, ceftazidime, cefepime, cefotaxime, and aztreonam each 30 μg per disk, and the following antimicrobial agents were tested: ampicillin, piperacillin-tazobactam, meropenem, aztreonam, ciprofloxacin, levofloxacin, gentamicin, amikacin, and trimethoprim-sulfamethoxazole by the disk diffusion test method. Quality control was conducted by using *Escherichia coli* ATCC 25922 and *E. coli* ATCC 35218. The double disc synergy test (DDST) according to the Clinical Laboratory Standard Institute (CLSI) guidelines (CLSI 2011) was used for extended-spectrum beta-lactamase (ESBL) detection of the strain and confirmation was performed by combination disk diffusion test using CAZ, CTX disks along with CAZ-CL, CTX-CL. The isolate was susceptible to amikacin, gentamicin, ciprofloxacin, co-trimoxazole (SXT), carbapenems, resistant to ampicillin, amoxicillin-clavulanic acid (AMC), and all cephalosporins. Antimicrobial susceptibility rates and MIC values of the antimicrobials were shown on Table 1. The isolate was ESBL-producer and therefore cefuroxime axetil treatment was stopped, and a new antibiotic regimen consisting of levofloxacin (500 mg IV once daily for 10 days) was chosen on the basis of the susceptibility tests.

The patient remained febrile at the second day of hospitalization. Within the following 48 h, marked improvement in the patient's clinical condition and inflammatory parameters was observed. A repeat sputum culture on the seventh day of the treatment showed no growth of gram-negative bacterial species and oral flora species were seen. The patient was discharged from the hospital with complete cure and any complicating infection was not detected.

Table 1 MICs and 2012 CLSI interpretations for the *E. cancerogenus* strain

Antimicrobial	MIC (μg/mL) by	CLSI interpretation	
	VITEK	VITEK	DD
Ampicillin	≥32	R	R
Amoxicillin/Clavulanic acid	≥32	R	R
Piperacillin/Tazobactam	≤4	S	S
Cefuroxime	≥64	R	R
Ceftazidime	≥64	R	R
Ceftriaxone	≥64	R	R
Ciprofloxacin	≤0.25	S	S
Ertapenem	≤0.5	S	S
Imipenem	≤0.25	S	S
Meropenem	≤0.25	S	S
Amikacin	≤2	S	S
Cefepim	≤1	S	S
Gentamicin	≤1	S	S
Levofloxacin	–	–	S
Co-trimoxazole	≤20	S	S

DD disc diffusion, *MIC* minimal inhibitor concentration, *R* resistance, *S* susceptible

Discussion

Enterobacter spp. are responsible for a variety of infections including bacteremia, lower respiratory tract infections, skin and soft-tissue infections, urinary tract infections (UTIs), endocarditis, intraabdominal infections, septic arthritis, and osteomyelitis. Up to date, 15 species in this genus were described; *Enterobacter cloacae* and *Enterobacter aerogenes* being the most common. These two species are routinely isolated from human, while the others are mostly isolated from environmental sources (Dickey and Zummoff 1988; Hart 2006). *E. cancerogenus* is a lactose-fermenting bacillus that has a DNA relatedness of 61 % to *E. cloacae* and differs from it mostly by being ornithine decarboxylase negative and D-arabinose positive. Strains of *E. cancerogenus* (formerly known as CDC Enteric Group 19; synonym with *Enterobacter taylorae*) are positive for Voges–Proskauer, citrate utilization, arginine dihydrolase, ornithine decarboxylase, motility, growth in KCN medium, and malonate utilization (Farmer and Davis 1985; Reina et al. 1989). Although *E. cancerogenus* is part of some patients' normal endogenous flora of skin, respiratory system, and gastrointestinal tract, it could be detected as an opportunistic pathogen after instrumentation or invasive procedure implementation that enabled bacterial invasion such as

biopsy, tracheal intubation, and urinary catheterization. *E. cancerogenus* has rarely been isolated from blood, osteomyelitis, spinal fluid, wounds, urine, respiratory tract, and stool specimens (Abbott 1999; Abbott and Janda 1997; Farmer et al. 1985; Martinez et al. 1994; Reina and Alomar 1989; Reina et al. 1989; Rubinstien et al. 1993; Westblom and Coggins 1987; Farmer et al. 1985; Garazzino et al. 2005). Patient age over 75 years, hospitalization for more than 48 h, could play a role in the infection development (Rubinstien et al. 1993). The use of cephalosporins outside the hospital may also contribute to the emergence and proliferation of this organism in the community, thus providing an additional avenue of introduction into the hospital microflora (Rubinstein et al. 1993). Prophylactic antimicrobial implementations prior to major surgeries revealed to the increase in gastrointestinal colonization of gram-negative bacteria such as *Enterobacter* spp. (Flynn et al. 1987). In this case, neither an invasive procedures nor clear environmental or common source of infection that could provide a portal of entry was defined. Only identified risk factor for the infection was frequent corticosteroid and antimicrobial medications due to the respiratory distress attacks and frequent antibiotic use prior and during influenza-like illness. In fact, we could not clearly identified whether *E. cancerogenus* was the causitive agent in the infection or not, but it is strongly considered as pathogen based on the evidence of gram-negative rod and dominancy of polymorphonuclear leukocytes observed in the gram-staining of sputum.

E. cancerogenus exhibits natural resistance to aminopenicillins and/or to narrow- and extended-spectrum cephalosporins (Ambler 1980; Rottman et al. 2002; Stock and Wiedemann 2002, Garazzino et al. 2005). The β-lactam phenotype of *E. cancerogenus* is similar to that expressed by other well-known *Enterobacter* spp. and indicates the presence of chromosomally encoded AmpC β-lactamases (Ambler 1980; Rottman et al. 2002; Stock and Wiedemann 2002; Garazzino et al. 2005). The constitutive hyperproduction of AmpC is of major concern, since it confers resistance to most β-lactam antibiotics, sparing only carbapenems and, amongst cephalosporins, only cefepime. This phenotype commonly results from selective antibiotic pressure (Garazzino et al. 2005; Bradford et al. 1997). Extended-spectrum β-lactamases (ESBLs) are found predominantly in *Klebsiella* species and *E. coli*, but have been described in other species as well, including *Enterobacter*, *Serratia*, *Citrobacter*, *Proteus*, and *Salmonella* (Paterson and Bonomo 2005). Previous reports indicate that extended-spectrum β-lactamases (ESBL) are increasingly prevalent in *Enterobacter* spp., posing a challenge to the treatment of infections caused by this microorganism, with the reported resistance rates of 20–35.6 % (Nogueira Kda et al. 2014; Garza-González et al. 2011). The Clinical and Laboratory Standards Institute (CLSI) has established guidelines for the detection of ESBLs in *E. coli*, *Klebsiella* spp., and *Proteus mirabilis*. However, there are no recommendations from the CLSI for detection of ESBLs in microorganisms with chromosomal AmpC β-lactamases since the presence of ESBLs can be masked by the AmpC β-lactamases (Kanamori et al. 2012; Nogueira Kda et al. 2014). Our strain displayed an antibiotic susceptibility pattern similar to previously reports (Reina et al. 1989; Rubinstien et al. 1993; Westblom and Coggins 1987). The strain was ESBL-producer but AmpC hyperproduction was not detected by phenotypic tests.

The aim of our brief report is primarily to contribute to the understanding of *E. cancerogenus* infections, to the knowledge of the epidemiology, clinical manifestations, and therapeutic options. In conclusion, we suggest that *E. cancerogenus* could play an important role in pneumonia as an opportunistic or a secondary pathogen especially among patients treated with corticosteroids. More studies should be conducted to achieve a better understanding regarding the epidemiology and clinical significance of this organism.

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Conflict of interest The authors declare that there is no conflict of interest.

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