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KLEBSIELLA PNEUMONIAE OXA-48 IN A UROLOGY PATIENT: CASE REPORT

Ines Jajić[1], Ana Benčić[2], Marko Siroglavić[3], Gernot Zarfel[4], Boris Ružić[5], Ivan Pezelj[5] and Branka Bedenić[6,7]

[1]Department of Microbiology, Parasitology and Hospital Infections, Sestre milosrdnice University Hospital Center; [2]School of Medicine, University of Zagreb; [3]Department of Transfusion Medicine, Zagreb University Hospital Center, Zagreb, Croatia; [4]Institute for Microbiology, Hygiene and Environmental Medicine, University of Graz, Graz, Austria; [5]Department of Urology, Sestre milosrdnice University Hospital Center; [6]Department of Microbiology, School of Medicine, University of Zagreb; [7]Clinical Department of Clinical and Molecular Microbiology, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – We present an isolate of *Klebsiella pneumoniae* OXA-48 isolated in a 68-year-old man who underwent radical prostatectomy due to prostate cancer. The antibiotic susceptibility testing to a wide range of antibiotics was performed by disk diffusion method and determination of minimal inhibitory concentrations. The isolate was classified as multidrug-resistant. It showed intermediate susceptibility to imipenem and meropenem, resistance to ertapenem, and sensitivity only to colistin, amikacin, and trimethoprim-sulfamethoxazole. The isolate was positive for ESBLs, negative for AmpC. Polymerase chain reaction and sequencing revealed $bla_{\text{OXA-48}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-11}}$. The plasmid encoding OXA-48 ß-lactamase did not belong to any known PCR-based replicon typing. According to genotyping, the isolate belonged to ST37.

Key words: *Klebsiella pneumoniae – isolation and purification; Klebsiella infections; Prostatectomy – complications; Case reports*

Introduction

Carbapenems are the drugs of choice for the treatment of infections caused by multiresistant gram-negative bacilli[1]. Carbapenemases involved in acquired resistance belong to Ambler class A serin ß-lactamases (KPC, SME, GES, IMI, NMC), class B metallo-ß--lactamases (MBL) of IMP, VIM or NDM family, or OXA-48-like ß-lactamases belonging to class D ß-lactamases[2].

Resistance phenotypes of carbapenemase producing *Enterobacteriaceae* (CRE) range from extreme multiresistance to resistance only to ß-lactams[2]. The first carbapenem-resistant *Enterobacteriacae* species in Croatia was NDM-1 producing *Klebsiella (K.) pneumoniae* isolated in 2008 at the Zagreb University Hospital Center[3]. Later on, in 2011, a KPC-2-positive *K. pneumoniae* was isolated at the same institution[4]. This observation gave rise to a multicenter study on carbapenem-resistance in *Enterobacteriaceae* in Croatia, conducted in 2011-2012, which revealed the predominance of VIM-1 ß-lactamase in two large hospital centers (Zagreb and Split), but only KPC ß-lactamase was reported at Sestre milosrdnice University Hospital Center[5]. In 2013, an outbreak of VIM-1 producing *Enterobacter (E.) cloacae* was reported at Split University Hospital Center[6]. Following emergence of KPC ß-lactamases in 2013, the first outbreak associated with KPC-2 was observed at Sestre milosrdnice University Hospital Center in 2014[7]. Carbapenemase-producing *Enterobacteriacae* were further identified in

Correspondence to: *Ines Jajić, MD*, Department of Microbiology, Parasitology and Hospital Infections, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: ines.jajic@kbcsm.hr

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Sestre milosrdnice University Hospital Center, posing serious therapeutic problem for the clinicians.

Carbapenemase producing *Enterobacteriaceae* often co-harbor resistance genes encoding extended-spectrum ß-lactamases (ESBLs), plasmid-mediated AmpC ß-lactamases and *qnr* genes responsible for reduced susceptibility to fluoroqinolones[2].

Sestre milosrdnice University Hospital Center is a hospital with 1200 beds in all medical specialties. It serves a great part of the Zagreb population and acts as a referral hospital for the whole Croatia for specific patients/procedure groups, thus covering a catchment population of about 4,000,000 people.

Case Report

A 68-year-old man without serious illnesses in his medical history and no prior hospitalization in other hospitals was admitted for the first time to Department of Urology, Sestre milosrdnice University Hospital Center, for elevated prostate specific antigen (PSA) level. During his first hospitalization, transrectal ultrasound guided prostate biopsy was performed. After biopsy, the patient experienced no discomfort or dysuria. His diuresis was regular and he was discharged home while expecting his histopathologic report. The antibiotic ciprofloxacin was prescribed one day prior to biopsy and for the next five days. The dosage was 500 mg two times daily. No urine cultures were performed prior to biopsy, as the patient reported no symptoms related to urinary tract infection.

Histopathologic finding revealed prostatic cancer and the patient was admitted for the second time. Radical prostatectomy was performed. The procedure was routine, with no complications. One hour prior to surgery, the patient received a single dose of 750 mg of cefuroxime. Since no fever was present during his stay at the Department and his routine urine culture sampled at admission was sterile, no further antibiotics were administered.

Two weeks after discharge from the hospital, the patient presented to the Department due to obstructive voiding symptoms. No dysuria or fever was present, so a Foley catheter was placed. One week after catheter placement, it was removed and the patient reported normal urine voiding. Abdominal ultrasound found no residual urine after voiding.

One month after surgical treatment, the patient was admitted to the Department as an emergency case. His diagnosis upon admission was as follows: urinary retention caused by urinary tract infection. Immediately upon admission to the same Department, his urine was sampled for microbiological analysis. The specimen was sent to Department of Microbiology, Parasitology and Hospital Infections, Sestre milosrdnice University Hospital Center and processed. Urine culture revealed *K. pneumoniae* in the quantity of 10^5. According to the zone diameter breakpoint in disk diffusion method, the *K. pneumoniae* isolate was resistant to the following antibiotics: ampicillin, amoxicillin-clavulanic acid, piperacillin-tazobactam, cefazolin, cefuroxime iv., ceftibuten, cefixime, ceftriaxone, ceftazidime, cefepime, ertapenem, norfloxacin, levofloxacin, ciprofloxacin, and gentamicin. It was susceptible to amikacin, trimethoprim-sulfamethoxazole and colistin (susceptibility to colistin was determined by E-test). The isolate showed intermediate susceptibility to imipenem and meropenem. The isolate of *K. pneumoniae* was sent to the Zagreb University Hospital Center for further investigation and OXA-48 ß-lactamase was identified.

Trimethoprim-sulfamethoxazole *per os* was administered. Urethrocystoscopy was done to exclude mechanical obstruction (e.g., bladder-urethra anastomosis sclerozation or bladder calculi) as the cause of urinary retention. No obstruction was found. Upon completion of antibiotic therapy, the patient had no residual urine after voiding, no pain during voiding, and was fully continent, suggesting a conclusion that urinary tract infection was the cause of urinary retention.

Hospital infection control measures were recommended, including isolation of the patient, cleaning of the ward and equipment, hygienic measures, use of gloves and gowns by medical personnel, etc.

Methods

Identification and antimicrobial susceptibility testing

The isolate of *K. pneumoniae* was identified using standard biochemical methods. The antibiotic susceptibility testing to a wide range of antibiotics was performed by disk diffusion method and broth microdilution method in 96-well microtiter plates and inter-

preted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints[8-10]. The isolate was classified as multidrug-resistant, extensively-drug-resistant or pan-drug-resistant according to Magiorakis *et al*.[11] .

Phenotypic tests for detection of ESBLs, plasmid-mediated AmpC ß-lactamases and carbapenemases

Double disk synergy test (DDST)[12] and CLSI combined disk test with the addition of clavulanic acid[10] were performed to detect ESBLs. Plasmid-mediated AmpC ß-lactamases were detected by combined disk test using cephalosporin disks combined with PBA (3-aminophenylboronic acid)[13]. Modified Hodge test (MHT) was used to screen for the production of carbapenemases[14]. Additionally, the isolate was tested by combined disk tests with imipenem and meropenem alone and combined with 3-aminophenylboronic acid test (PBA), 0.1 M EDTA or both to screen for KPC, MBLs, or simultaneous production of KPC and MBL, respectively[15,16].

Conjugation

The transferability of meropenem resistance was determined by conjugation (broth mating method) employing *E. coli* A15R$^-$ strain resistant to rifampicin and *E. coli* J65 resistant to sodium azide[17]. Transconjugant was selected on combined plates containing meropenem (1 mg/L) to inhibit the growth of recipient strain and rifampicin (256 mg/L) or sodium azide (100 mg/L) to suppress donor strains.

Molecular detection of resistance genes

The genes conferring resistance to ß-lactams including broad spectrum and extended-spectrum ß-lactamases (bla_{SHV}, bla_{TEM}, bla_{CTX-M} and bla_{PER-1})[18-22], plasmid-mediated AmpC ß-lactamases[23], class A carbapenemases (bla_{KPC}, bla_{SME}, bla_{IMI} and bla_{NMC},)[24-26], class B ($bla_{VIM,}$ bla_{IMP} and bla_{NDM})[27-29], and carbapenem hydrolyzing oxacillinases (bla_{OXA-48})[30] and to fluoroquinolones (*qnr*A, *qnr*B and *qnr*S)[31] were determined by PCR using protocols and conditions as described previously. The DNA was extracted by boiling method. Amplicons were column-purified with Qiagen DNA purification kit (Inel, Zagreb, Croatia) and sequenced directly in Eurofin sequencing service (Ebersberg, Germany).

Characterization of plasmids

Plasmids were extracted with Qiagen Mini kit according to the manufacturer's instructions. PCR-based replicon typing (PBRT) according to Carattoli *et al*.[32] was applied to type the resistance plasmids carrying carbapenemase genes.

Genotyping

The isolate was also genotyped by MSLT according to Diancourt *et al*.[33].

Results

Antimicrobial susceptibility testing

Determination of minimal inhibitory concentrations (MICs) revealed resistance to amoxicillin alone and combined with clavulanic acid, piperacillin, piperacillin/tazobactam, cefazolin, cefuroxime, ceftazidime, cefotaxime and cefepime with MIC of >128 mg/L, ertapenem (16 mg/L), gentamicin (>128 mg/L) and ciprofloxacin (32 mg/L), as shown in Table 1. Meropenem and imipenem showed intermediate susceptibility (2 mg/L).

Table 1. Minimal inhibitory concentrations (MICs) of various antibiotics for Klebsiella pneumoniae isolate

Antibiotic	MIC (mg/L)
Amoxycillin	>128
Amoxycillin/clavulanate	>128
Piperacillin	>128
Piperacillin/tazobactam	>128
Cefazoline	>128
Cefuroxime	>128
Ceftazidime	>128
Cefotaxime	>128
Ceftriaxone	>128
Cefepime	>128
Ertapenem	16
Imipenem	2
Meropenem	2
Gentamicin	>128
Ciprofloxacin	32
Colistin	0.032

Phenotypic tests for detection of ESBLs, plasmid-mediated AmpC ß-lactamases and carbapenemases

The isolate was positive for ESBLs in inhibitor based test with clavulanic acid (an increase of inhibition zone around cephalosporin disks in the presence of clavulanate for 10 to 15 mm), but negative for AmpC in inhibitor based test with phenylboronic acid.

Conjugation

The *K. pneumoniae* isolate did not transfer meropenem resistance to *E. coli* recipient strain.

Molecular detection of resistance genes

Polymerase chain reaction and sequencing revealed $bla_{\text{OXA-48}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-11}}$ with the latter being chromosomally encoded in *K. pneumoniae*.

Characterization of plasmids

The plasmid encoding OXA-48 ß-lactamase did not belong to any known PBRT.

Genotyping

The isolate belonged to ST37.

Discussion

We report a case of urinary tract infection in a patient with prostate cancer associated with *K. pneumoniae* positive for OXA-48 ß-lactamase. OXA-48 was first reported in Turkey in 2001[30,34], but later it spread in many European countries such as France[35,36], Israel[2], Italy[37], Spain[38], Germany[39], Switzerland[2], Belgium[40], The Netherlands[41], Ireland[42], Sweden, Denmark, Norway, Finland[2] and also in Slovenia[43] as a Croatia neighbor country. In Belgium and The Netherlands, it is the most prevalent type of carbapenemase. Croatia was spared from this type of carbapenemase until 2014. Our *K. pneumoniae* with OXA-48 *K. pneumoniae* originating belonged to ST37, unlike UK where it belonged to ST221[2], The Netherlands and France where it was allocated to ST395, and Belgium where it belonged to ST147[36,40]. Laboratory detection of OXA-48 ß-lactamase poses a serious problem because of the low level carbapenem resistance and sometimes lack of additional ESBL. In our report, the strain had elevated carbapenem MICs co-harbored CTX-M-15 ß-lactamase, which is responsible for resistance to expanded-spectrum cephalosporins. The majority of OXA-48 producing European isolates coproduce CTX-M-15 or SHV-12 ß-lactamase[38]. OXA-48 ß-lactamase is usually plasmid-mediated and the majority of plasmids encoding it belong to W, P or L/M incompatibility group[2,38]. Transposon Tn1999 is responsible for the mobilization of $bla_{\text{OXA-48}}$ gene[36]. However, our isolate did not transfer resistance to *E. coli* recipient strain and the plasmid extraction did not yield any product in PCR for plasmid incompatibility typing. PCR for *qnr* genes was negative indicating that fluoroquinolone resistance was probably due to other mechanism such as mutations in *gyr*A or *par*C genes.

Microbiological laboratories should be able to detect and characterize carbapenemase producing *Enterobacteriaceae* in order to prevent the spread of these important 'superbugs'.

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Sažetak

KLEBSIELLA PNEUMONIAE OXA-48 KOD UROLOŠKOG BOLESNIKA: PRIKAZ SLUČAJA

I. Jajić, A. Benčić, M. Siroglavić, G. Zarfel, B. Ružić, I. Pezelj i *B. Bedenić*

Prikazan je izolat *Klebsiella pneumoniae* OXA-48 izoliran iz mokraće 68-godišnjeg muškaraca kojemu je napravljena radikalna prostatektomija zbog raka prostate. Testiranje osjetljivosti izolata na velik broj antibiotika provedeno je metodom disk difuzije kao i metodom određivanja minimalnih inhibitornih koncentracija. Izolat je klasificiran kao višestruko rezistentan. Smanjeno je osjetljiv na imipenem i meropenem, rezistentan na ertapenem, a osjetljiv samo na kolistin, amikacin i trimetoprim+sulfometoksazol. Izolat proizvodi ESBL, a ne proizvodi AmpC. Lančana reakcije polimeraze i sekvenciranje je pokazalo $bla_{\text{OXA-48}}$, $bla_{\text{CTX-M-15}}$ i $bla_{\text{SHV-11.}}$ Plazmidno kodirana OXA-48 ß-laktamaza ne pripada niti jednom poznatom PBRT. Prema genotipizaciji, izolat pripada ST37.

Ključne riječi: *Klebsiella pneumoniae – izolacija i purifikacija; Klebsiella infekcije; Prikazi slučaja*