Detection of OXA-51 Carbapenemase Gene in *Klebsiella pneumoniae*: A Case Report and a New Dimension on Carbapenemase Resistance

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Abstract

We investigated the occurrence of genes associated with the production of carbapenem hydrolysing carbapenemases in *Klebsiella pneumoniae* isolates recovered from ICU patient. Antimicrobial susceptibility testing was performed and resistance genes were characterized by PCR amplification and sequencing. The Modified Hodge Test (MHT), MBL E-test, EDTA and aminopenicillanic acid (APBA) combined disk diffusion method, and a disk enzymatic assay were performed for the screening of carbapenemases. MICs of carbapenemases were as follows: (mgl.) ertapenem 0.06, meropenem 0.25 and doripenem 0.5. The isolate demonstrated positive results in the ESBL, EDTA and APBA combined tests, and disk enzymatic assay. PCR and sequencing revealed the presence of bla*OXA-51* and bla*CTX-M-15*, beta-lactamase genes. Plasmids were not transferred to recipient *E. coli* by conjugation and transformation. In conclusion, we report on the first detection of the OXA-51 harboring *K.pneumoniae* isolate and co-produced a CTX-M-15 β-lactamase.

Keywords: *Klebsiella pneumoniae*, OXA-51 carbapenemase; Carbapenems; CTX-M-15 β-lactamase; OXA genes

Introduction

Carbapenemase related resistance against carbapenems is a serious threat and cause of treatment failure especially for patients infected with hospital strains. Carbapenem resistance was rarely reported in enteric bacteria until recent years. In Enterobacteriaceae, carbapenemases are diverse problem; these belong to molecular class B (IMP, VIM or NDM), class A (KPC) and class D (OXA-23 and OXA-48) enzymes as well as those combining AmpC enzyme or an extended-spectrum β-lactamase (ESBL) with porin loss. These carbapenemases are involved in outbreaks in various geographical regions and are increasingly reported in sporadic cases worldwide [1-6]. OXA carbapenemases are responsible for middle level carbapenem resistance mostly among *Acinetobacter* spp. Previously, OXA-23, OXA-24/40, OXA-58 were reported in sporadic cases worldwide [1-6]. OXA-51 carbapenemase was identified from a 31-year-old male suffering from Miller-Fisher syndrome was admitted to Neurology intensive care unit (ICU). Nine days after his admission, he suffered from ventilator-associated pneumonia. Carbapenem resistance was rarely reported in ICU patient. Antimicrobial susceptibility testing was performed and resistance genes were characterized by PCR amplification and sequencing. The Modified Hodge Test (MHT), MBL E-test, EDTA and aminopenicillanic acid (APBA) combined disk diffusion method, and a disk enzymatic assay were performed for the screening of carbapenemases. MICs of carbapenemases were as follows: (mgl.) ertapenem 0.06, meropenem 0.25 and doripenem 0.5. The isolate demonstrated positive results in the ESBL, EDTA and APBA combined tests, and disk enzymatic assay. PCR and sequencing revealed the presence of bla*OXA-51* and bla*CTX-M-15*, beta-lactamase genes. Plasmids were not transferred to recipient *E. coli* by conjugation and transformation. In conclusion, we report on the first detection of the OXA-51 harboring *K.pneumoniae* isolate and co-produced a CTX-M-15 β-lactamase.

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In the present study, we investigated the occurrence of genes associated with the production of carbapenem hydrolysing carbapenemases in *Klebsiella pneumoniae* isolates recovered from inpatient at Hospital, a 1000-bed training hospital located in Istanbul.

Case Report

At the end of March 2010, a 31-year-old male suffering from Miller-Fisher syndrome was admitted to Neurology intensive care unit (ICU). Nine days after his admission, he suffered from ventilator-associated pneumonia. A strain of *Acinetobacter baumannii* was isolated from tracheal aspirate sample. The patient was treated with a broad spectrum beta-lactam and beta-lactamase inhibitor combination for *Acinetobacter baumannii*-related, ventilator-associated pneumonia. However, the patient on prolonged mechanical ventilation, another VAP was diagnosed caused by ESBL producing *K. pneumoniae* that was resistant to ertapenem was isolated from tracheal aspirate and blood cultures on the 25th day of stay. The patient was successively treated with colistin (10 days) for ertapenem resistant *K. pneumoniae*. He was discharged. in good health from the hospital 50 days after admission (Table 1).
(DDST). In addition, a disk enzymatic assay was performed to detect carbapenemase production [13].

### Genotypic characterization

The presence of carbapenemase-encoding genes was investigated by polymerase chain reaction (PCR) and sequencing. Genes encoding production of serine carbapenemases (*bla*~KPC~), Class B (*bla*~IMP~, *bla*~VIM~, *bla*~OXA-23~, *bla*~OXA-48~), OXA beta lactamases genes (*bla*~OXA-23, like~, *bla*~OXA-48~) were analysed with a set of primers that amplify specific segments of individual beta-lactamases [14-20]. In addition, several extended-spectrum β-lactamases (PER-1, TEM, SHV and CTX-M) and acquired AmpC and Qnr genes (*qnrA*, *qnrB*, *qnrS*) were investigated by PCR [21-26]. For the detection of class 1 integron cassettes, integron PCR was performed with primers 5’ CS and 3’ CS, as described previously [27]. PCR products were analysed by electrophoresis in a 1.5% agarose gel containing 0.5 mg/L ethidium bromide at 120V for 60 minute.

### Plasmid analysis

Plasmid DNA extraction was attempted by the Kado Liu method [28]. Plasmid extracts were subsequently analysed by electrophoresis on a 0.7% agarose gel at 100 V for 4 hours using the plasmids extracted from *E. coli* VS17 as the standard marker.

### Transfer of resistance

Conjugation was performed using *Escherichia coli* J53 Azt as the recipient strain. Mac Conkey and EMB agar plates supplemented with sodium azide (100 mg/L), cefazidime (0.5 mg/L) and imipenem (0.125 mg/L) were used. Transformants were selected on Mueller-Hinton agar plates supplemented with 100 mg/L ampicillin, 2mM IPTG and 2% X-galactose and screened to harbor corresponding OXA-51 and CTX-M-15 genes multiplex PCR assay.

### Results

**K. pneumoniae isolate** was resistant to all β-lactams including ertapenem, to all aminoglycosides, to fluoroquinolones and to trimethoprim/sulfamethoxazol (Table 2). MICs of carbapenemes were as follows (mg/L) ertapenem 8, meropenem 1, imipenem 0.25 and doripenem 0.5. It was susceptible to tigecycline and colistin (MICs of 0.5 μg/ml for both). The isolate demonstrated positive results in the ESBL, EDTA and APBA combined tests, and disk enzymatic assay. However, no KPC and MBL genes were detected. Acquired AmpC-type beta-lactamases and Qnr genes were not found. PCR and sequencing revealed the presence of, *bla*~OXA-51~, and *bla*~CTX-M-15~ beta-lactamase genes. Plasmid analysis indicated the presence of two plasmids (40 and 1.2 kb).

**Transfer of resistance**

Plasmids extracted *K. pneumoniae* strain were not transferred to recipient *E. coli* by conjugation. Transforming or transconjugant harbouring the *bla*~OXA-51~ gene were not obtained, which could have suggested a chromosomal location of gene.

### Discussion

Reports in the United States and Europe point out the major problem caused by enteric bacteria with metallo-beta-lactamase (MBL) and KPC related carbapenem resistance [1,3-6]. The emergence and the spread of acquired carbapenem-hydrolysing class D beta-lactamases (CHDLs) have been well documented worldwide. There are nine major subgroups of OXA carbapenemases, based on amino acid homologies in Gram negative bacteria. Subgroups 1 (OXA-23-like), 2 (OXA-24-like), 3 (OXA-51-like) and 4 (OXA-58) frequently detected *A. baumannii* [29]. The plasmid-mediated OXA-48 enzyme, which forms the sixth subgroup, has been found primarily in *K. pneumoniae*, *E. coli*, *C. freundii* and *E. cloacae* [19, 30]. Among the genes encoding OXA-type carbapenemases; *bla*~OXA-51~, *bla*~OXA-23~, and *bla*~OXA-48~ found in *A. baumannii* and *bla*~OXA-58~ found in *K. pneumoniae* are plasmid-born, while OXA-51 may be naturally occurring in *A. baumannii*. However, a plasmid-born 15Aba1-bla(OXA-51)-like gene has recently been identified in *Acinetobacter* genomic species 13TU and in several *A. baumannii* isolates [7,8]. With regard to the mechanism of carbapenem resistance in Turkey, KPC gen was not detected in any of the studied isolates. In contrast, the genes encoding CHDLs (OXA-51, OXA-23, OXA-58) were detected in multidrug resistant *Acinetobacter* spp in several centers. In addition, OXA-48 carbapenemase is not rare especially among *K. pneumoniae* strains isolated from hospital infections [30].

Rapid identification of carbapenemase-producing, Gram-negative species is crucial for timely implementation of infection control measures. A previous survey carried out in our hospital in 2010, demonstrated that the *bla*~OXA-23~ and *bla*~OXA-51~ genes were prevalent enzymes associated with carbapenem resistance in multidrug resistant *A. baumannii* isolates. All were positive for the *bla*~OXA-51~ like genes as well (unpublished data). Data concerning carbapenem resistance among Enterobacteriaceae in our hospital, the percentage of ertapenem-resistant strains of *K. pneumoniae* was 10% in 2010. OXA-48-type oxacillinase was found responsible for carbapenem resistance. Carbapenemases do not always produce resistant breakpoints for carbapenem when standardized susceptibility testing methods are employed. Effective treatment and infection control depend upon the rapid and efficient identification of these isolates.

MICs of ertapenem, imipenem and meropenem are greater than 0.5 and 2.0 mg/L, respectively may indicate isolates with carbapenemase production (9). Ertapenem resistance is the most sensitive screening test to detect KPC and MBL carbapenemases. On the other hand, there are a number of phenotypic tests which have been developed to detect these enzymes in Gram negative bacteria. The Modified Hodge Test (MHT) has been developed to detect both KPC and MBL enzymes, but it cannot differentiate between them; moreover, there are reports of false-positive results with CTX-M-positive or AmpC-hyperproducing Enterobacteriaceae. Several versions of boronic acid, an EDTA disk test and Etest with imipenem/iminipenem with EDTA have been used for detections for MBL carbapenemases. However, no currently available test allows detection of CHDLs. In the present study, *K. pneumoniae* was found resistant to ertapenem (8 mg/L). The isolate demonstrated...
positive results in the ESBL, EDTA and APBA combine tests, and disk enzymatic assay. However, unexpected results were detected as PCR and sequencing revealed the presence of \(\text{bla}_{\text{OXA-51}}\) gene in \(K.\) pneumoniae strain for the first time which are known to be \(A.\) baumannii-related. The isolates also possess \(\text{bla}_{\text{CTX-M-15}}\) beta-lactamase gene. Acquired AmpC-type beta-lactamas and \(qnr\) genes were not found. It is known that OXA enzymes do hydrolyze penicillins, but do not hydrolyze expanded-spectrum cephalosporin. They are responsible for low or middle level carbapenem resistance mostly among \(Acinetobacter\) spp. and are not inhibited by clavulanic acid but are inhibited by \(\text{NaCl}\) in \textit{vitro}. In the present study, \(K.\) pneumoniae strain was found to be susceptible to imipenem meropenem and doripenem on the basis of their MICs, which raises two issues: first, carbapenem-susceptible or decreased susceptibility and intermediate susceptible isolates may go clinically undetected during routine antibiotic drug susceptibility testing, second, the clinical efficacy of imipenem on such strains is uncertain.

OXA enzymes may be widespread rapidly among various Gram-negative bacteria. The dissemination of plasmids, transposons, and integrons among bacteria and species give rise to so-called gene epidemics. Integrons have a fearsome capacity for the recruitment, spread, and expression of resistance genes, and surveys show that they are widespread among gram-negative bacteria [6,7]. Chromosomal mediation of \(\text{bla}_{\text{OXA-23}}\) has been described previously for \(P.\) mirabilis [1].

In the present study, the patient firstly infected MDR-\(A.\) baumannii and treated with a broad spectrum beta-lactam and beta-lactamase inhibitor combination for \(A.\) baumannii-related, VAP. However, 15 days later, a carbapenem resistant \(K.\) pneumoniae isolate was obtained from the same patient with VAP. We suggest that \(A.\) baumannii which possesses OXA-51 gene (data not shown) may be a source of carbapenem hydrolyzing oxacillinlases. These gene may have been inserted in the chromosome probably by genetic events of recombination, cointegration, or transposition \textit{in vivo}. After repeated attempts, conjugation experiments failed to demonstrate the transferability of plasmids in the strain. However, PCR also detected the presence of class 1 integrons (>1300 bp) for \(K.\) pneumoniae, and it was concluded that there were also other risk factors for antimicrobial resistance such as prior antibiotic treatment, ICU admission and severe underlying diseases.

OXA-48-producing \(K.\) pneumoniae strains have been identified also in the same hospital during the same period of time. Affected wards were cleaned daily appropriate disinfectant, universal contact precautions were applied and there were three times of education clinical staff in affected wards. Environmental screening was implemented once a week. Within 24 hours after admission, rectal swabs or stool specimens were collected from patients for identification of carbapenem-resistant Enterobacteriaceae.

In conclusion, our report confirms the first detection of the OXA-51 harboring \(K.\) pneumoniae isolate and co-produced a CTX-M-15 \(\beta\)-lactamase. As it has already mentioned above, due to the fact that OXA-beta-lactamases remains difficult to detect by phenotypic tests, enhanced surveillance and rapid identification are essential. The ability to limit the spread of these pathogens will require effective laboratory screening methods to quickly identify patients infected with these organisms. Laboratories will need new tools, perhaps molecular techniques in order to make the process quicker and more accurate. It is highly significant to immediately introduce specific infection control measures in hospital settings in order to limit the nosocomial spread of these strains.

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| MIC (mg/L) | IP   | MEM  | ETP  | DOR  | TM   | AK   | FX   | TX   | XL   | TZ   | PTC | XM | AM | CPS | CT | OF |
|----------|------|------|------|------|------|------|------|------|------|------|-----|----|----|-----|----|----|
| K.pn-38  | 0.25 | 1    | 8    | 0.5  | 96   | 128  | >256 | >256 | >256 | >256 | >256 | >16 | >32| >32 |
| Transformant-38 | 0.25 | 0.23 | 0.16 | 0.23 | 0.38 | 1    | 0.064| 24/12| 1    | 3/4  | 4   | >256| 4  | 0.032| 0.008|
| \(E.\) coli DH10B | 0.125 | 0.16 | 0.08 | 0.12 | 0.38 | 2    | 2    | 0.094| 3/1.5| 0.19 | 1/4 | 3   | 0.016| 0.032| 0.16|
| \(E.\) coli DH10B (PUC19) | 0.125 | 0.16 | 0.06 | 0.12 | 0.38 | 1.5 | 1.5 | 0.047| 0.016 | 3/4 | 2   | >256| 4  | 0.016 | 0.047|

Table 2: MIC (mg/L) distribution of imipenem (IP), meropenem (MEM), ertapenem (ETP), doripenem (DOR) tobramycin (TM), cefotaxime (FX), amikacin (AK), ceftriaxone (TX), amoxicillin/clavulanic acid (XL) cefazidime (TZ), piperacillin/tazobactam (PTC), cefuroxime (CXM), ampicillin (AM), ceftizoxime/subactam (CPS), cephalotin (CT) ofloxacin (OF) for \(K.\) pneumoniae and transformant-38.
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