Successful Treatment of Urinary Tract Infection in Kidney Transplant Recipients Caused by Multiresistant *Klebsiella pneumoniae* Producing New Delhi Metallo-Beta-Lactamase (NDM-1) With Strains Genotyping

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ABSTRACT

Background. *Klebsiella pneumoniae* New Delhi metallo-beta-lactamase-1 (NDM-1) strains have recently become a new threat in kidney transplant recipients due to the strains' resistance to almost all antibiotics, including carbapenems.

Methods. We present a case series of 3 patients with urinary tract infections (UTIs) caused by multiresistant *K pneumoniae* NDM-1 strains who were treated with the same protocol. Genotyping sequencing with pulsed-field gel electrophoresis was performed in all cases.

Results. All patients were male and had undergone kidney transplantation 4, 7, and 8 months, respectively, before the admission. Combined antibiotic therapy consisting of imipenem/cilastatin in maximal doses, gentamicin and/or colistin for 21 to 27 days, followed by oral fosfomycin, was used in all cases. There were no further UTI episodes in 2 patients at the 12-month visit. Three months after initial treatment, the third patient presented with leukocyturia with no clinical symptoms and a urine culture positive for *K pneumonia* NDM-1 strain. Interestingly, the strain was susceptible to trimethoprim/sulfamethoxazole despite resistance in previous urine culture samples. The patient was successfully treated with trimethoprim/sulfamethoxazole 2 × 960 mg/d for 3 weeks followed by 480 mg/d and 3 doses of fosfomycin. Genotyping sequencing revealed identical DNA restriction fragments in bacterial strains from 2 patients. In the third case, although a difference in 2 restriction fragments was observed, the strain was considered related to the others.

Conclusions. In cases of UTI caused by *K pneumoniae* NDM-1 strains, prolong combined treatment followed by oral fosfomycin prophylaxis can be successful. Strain genotyping should be performed to optimize further treatment protocols in such cases.

INFECTIONS caused by *Klebsiella pneumoniae* are common among kidney transplant recipients; however, no carbapenem-resistant cultures have been detected in the last 10 years [1]. A new carbapenem-resistant *K pneumoniae* strain producing New Delhi metallo-beta-lactamase-1 (NDM-1) was described by Yong et al [2] in 2009. The first case of a urinary tract infection (UTI) in a kidney transplant recipient caused by *K pneumoniae* resistant to all β-lactam drugs in Poland was described in 2014 and, in this patient, the infection resulted in graft loss [3]. An increase in the number of infections with *K pneumoniae* producing NDM-1 is both an epidemiologic and a clinical issue because there are no guidelines regarding the correct choice of an antibiotic or duration of treatment [4].

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The present case series describes 3 kidney transplant recipients who were admitted to our center with deterioration in graft function due to a UTI caused by NDM-1–producing *K pneumoniae*. The similarity of the isolates was analyzed by using molecular typing. All 3 patients were successfully treated with a similar protocol recently implemented in our center for infections caused by multidrug-resistant strains of *K pneumoniae*.

PATIENTS AND METHODS

Patients were included who underwent kidney transplantation in the Department of General, Vascular and Transplant Surgery, Medical University of Warsaw (Warsaw, Poland), in 2014 and hospitalized in the Department of Immunology, Transplantology and Internal Medicine due to graft function deterioration in the course of a UTI caused by NDM-1–producing *K pneumoniae* after transplantation. Blood and urine tests and kidney graft ultrasound were performed according to routine procedures. Urine, blood, and anal smears for bacteriologic evaluation were obtained from the patients on admission and at discharge. Urine culture, identification, antimicrobial sensitivity testing, and confirmation of the presence of the *ndm* gene, as well as molecular typing, were performed in the Department of Medical Microbiology. The urine cultures were conducted in accordance with national recommendations.

After detection of bacteriuria, identification to the species level and susceptibility tests were performed by using the Vitek 2 system (bioMèrieux, Marcy l'Étoile, France). Interpretation of drug resistance was performed according to the European Committee on Antimicrobial Susceptibility Testing guidelines. In addition, phenotypic tests were conducted for extended-spectrum β-lactamase, metallo-β-lactamase (MBL), and *K pneumoniae* carbapenemase (KPC) according to national recommendations. To confirm the carbapenem-resistant, MBL-positive strains, polymerase chain reaction with primers detecting the *ndm* gene was performed (NDM-1-F: 5′-GGTGCATGCCCGGTGAAATC-3′ and NDM-1-R: 5′-ATGCTGGCCTTGGGGAACG-3′) [5]. Amplification was performed in 50 μL and the following cycling parameters: initial denaturation at 95°C for 5 minutes; denaturation at 95°C for 30 seconds, annealing at 57°C for 30 seconds, and extension at 72°C for 1 minute, repeated for 31 cycles; and final extension step at 72°C for 7 minutes.

The restriction fragment length polymorphism in pulsed-field gel electrophoresis (PFGE) was employed. The enzyme XbaI (Fermentas, Vilnius, Lithuania) was used, and the protocol was elaborated based on the standardized PulseNet protocol for *Escherichia coli* O157:H7, *Salmonella*, and *Shigella* [6,7]. PFGE was performed in the CHEF-DR II system (Bio-Rad Laboratories, Hercules, Calif, United States). The gels were visually analyzed, and interpretation was performed according to the method evaluated by Tenover et al [8].

RESULTS

Case 1

A 59-year-old patient with end-stage renal failure caused by chronic glomerulonephritis underwent kidney transplantation on February 12, 2014. The posttransplant period was complicated by perigraft hematoma and reoperation. The patient was diagnosed with a UTI caused by MBL-producing *K pneumonia* 2 weeks after surgery, and he was treated with colistin, meropenem, and amikacin. Two months after transplantation, the patient was admitted to the hospital with fever, leukocyturia, and impaired graft function. Results of the urine culture revealed *K pneumoniae* producing NDM-1 confirmed by results of genetic testing (April 11, 2014) (Table 1).

The patient was treated with imipenem/cilastatin for 27 days and colistin for 21 days; he also received 3 g of fosfomycin orally on discharge with 2 consecutive doses every 7 days. Results of the checkup urine cultures detected no bacteria. The follow-up urine and anal smear cultures revealed MBL-producing *K pneumoniae* (not NDM-1); however, there were no clinical or laboratory signs of UTI. It was therefore concluded that the urine sample was contaminated with bacteria originating from the gastrointestinal tract (July 10, 2014). There were no recurrences of bacteriuria or UTIs during the 12-month follow-up.

Case 2

A 55-year-old patient with end-stage renal failure due to hypertensive nephropathy underwent kidney transplantation on February 14, 2014. Surgical reanastomosis was performed because of ureter stenosis 4 months later. The patient was admitted to the hospital with fever and impaired graft function 8 months after transplantation. *K pneumoniae* producing MBL was initially detected from the urine culture obtained on admission, and treatment with gentamicin and imipenem/cilastatin was initiated.

The final result of the urinary culture, confirmed by genetic testing, revealed a *K pneumoniae* strain producing NDM-1 (October 21, 2014) (Table 1) and, because of high resistance to imipenem, the drug was replaced with colistin. Combined treatment with gentamicin was administered for 22 days, imipenem/cilastatin for 8 days, and colistin for 14 days. Additional treatment was given with 3 g of fosfomycin orally on discharge, with consecutive doses every 7 days for 6 weeks. Results of the follow-up urine culture were negative, and no signs of UTI were detected during the 12-month follow-up in the outpatient clinic.

Case 3

A 66-year-old patient with end-stage renal failure in the course of hypertensive nephropathy underwent kidney transplantation on February 2, 2014. The posttransplant period was complicated by cholelithiasis, which resulted in a cholecystectomy and a UTI caused by MBL-producing *K pneumoniae*, which was treated with colistin, meropenem, and amikacin. On outpatient follow-up visits, the patient presented with persistent pyuria but with no other symptoms of UTI and no deterioration of graft function. However, *K pneumoniae* producing MBL were detected in urine cultures (June 16, 2014, and July 9, 2014) (Table 1), and the patient was treated with oral fosfomycin.

During the next control visit, the patient presented with fever, significant pyuria, and a positive urine culture finding (August 20, 2014). He was admitted to the hospital