Case Report

Urinary Catheter Colonization by Multidrug-Resistant Cedecea neteri in Patient with Benign Prostatic Hyperplasia

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1. Introduction

The Cedecea genus comprises facultatively anaerobic, Gram-negative bacilli that belong to the family Enterobacteriaceae [1]. Formerly classified as CDC Enteric Group 15, this genus currently contains three validly described species (Cedecea neteri, Cedecea lapagei, and Cedecea davisae) and two unnamed species (Cedecea sp. 3 and Cedecea sp. 5) [2]. Cedecea species have not been reported to cause invasive infection in healthy individuals, but are considered to be opportunistic pathogens due to their clinical isolation from severely immunocompromised patients. Documented infections associated with C. davisae include bacteremia in patients with cancer [3], chronic renal disease, [4] and diabetes mellitus [5], as well as a scrotal abscess in an individual with chronic heart disease and alcoholic hepatitis [6]. C. lapagei has been reported to cause pneumonia in patients with acute promyelocytic leukemia [7], chronic obstructive pulmonary disease [8, 9], and hypoxic ischemic encephalopathy [10]. To date, C. neteri has been reported previously in only three documented clinical cases: a bacteremic patient with valvular heart disease [11], a systemic lupus erythematosus individual who developed an acute flare-up with bacteremia due to C. neteri [12], and a patient with a polymicrobial peritonitis infection following abdominal surgery [13]. In those cases involving C. neteri, the infection spread rapidly and caused a life-threatening situation.

We describe the first reported case of an antibiotic-resistant C. neteri strain isolated from the urinary catheter of an elderly patient with benign prostatic hyperplasia and chronic kidney disease. The availability of a completely sequenced C. neteri genome [14] presents an opportunity to explore the genetic basis of antibiotic resistance by this potentially emerging opportunistic pathogen.
2. Case Presentation

An 88-year-old male presented to a large community teaching hospital with a primary complaint of an irritating, generalized skin rash. The patient was afebrile. He reported recently receiving vancomycin and piperacillin-tazobactam at another area hospital for lower extremity cellulitis. Due to the extensive nature of the skin rash, he was admitted for further clinical assessment.

The patient's past medical history was significant for hypertension, benign prostatic hyperplasia (BPH), stage 3 chronic kidney disease (CKD) (baseline serum creatinine, 1.8 mg/dL), class 3 obesity (BMI 43), cholecystectomy, and left knee replacement surgery. Due to BPH progression, the patient had been using a Foley catheter for the past year which was changed monthly.

Initial laboratory results were unremarkable except for a slightly decreased red blood cell (RBC) count of 3.97 × 10^6/µL, hemoglobin 11.9 g/dL (reference range, 13.5–8.0 g/dL), and hematocrit 36.5% (40.5–54.0%). His serum creatinine was slightly decreased red blood cell (RBC) count of 3.97 × 10^6/µL, hemoglobin 11.9 g/dL (reference range, 13.5–8.0 g/dL), and hematocrit 36.5% (40.5–54.0%). His serum creatinine was 2.02 mg/dL with an estimated glomerular filtration rate of 31 mL/min/1.73 m² and elevated blood urea nitrogen (BUN) of 37 mg/dL (7–18). Urinalysis revealed a clear, yellow appearance, trace leukocyte esterase, 2+ white blood cell (WBC) count, 2+ RBC, occasional bacteria, and <1 squamous epithelial cells. An initial urine culture produced no growth after 24 hours.

The patient's skin rash, which covered more than fifty percent of his body, was treated with intravenous methylprednisolone 60 mg every 8 hours along with diphenhydramine 25 mg every 8 hours as needed. As the rash improved, the methylprednisolone was changed to oral prednisone (40 mg/day). During treatment, the patient experienced an increase in serum creatinine to 2.49 mg/dL and a BUN of 100 mg/dL. Oral prednisone was tapered to 20 mg/day, and the patient's rash improved with treatment.

During hospitalization, the patient's WBC count became elevated to 12.6, but he remained afebrile. His Foley catheter was changed, and urinalysis from the catheter was performed. Urinalysis demonstrated a cloudy, yellow appearance, 3+ leukocyte esterase, 1+ RBC, 4+ WBC clumps, and 2+ bacteria. Urine Gram stain and culture results revealed catheter colonization by Gram-negative rods with a final result of >100,000 colony-forming units/mL of Cedecea neteri. No other microorganism was identified from the catheter. The patient received empirical therapy of intravenous aztreonam (500 mg/8 h) until antibiotic susceptibility evaluations performed using the MicroScan WalkAway 96 Plus (Beckman Coulter) enabled de-escalation of therapy. MIC determination revealed that the C. neteri isolate was sensitive to piperacillin-tazobactam, ceftazidime, ceftriaxone, cepefeme, aztreonam, gentamicin, tobramycin, nitrofurantoin, ciprofloxacin, and sulfamethoxazole-trimethoprim, but resistant to ampicillin, ampicillin-sulbactam, cefazolin, and cefoxitin, and intermediate to cefuroxime. The patient's WBC count returned to normal range, and therapy was de-escalated to ciprofloxacin 250 mg twice daily for 5 days prior to the patient's discharge to a rehabilitation facility.

3. Discussion

We describe a multidrug-resistant C. neteri strain isolated from the urinary catheter of an elderly patient with long-term catheterization due to progressive prostatic hyperplasia. Because C. neteri is capable of causing bacteremia in immunocompromised individuals [11, 12], the patient in this case was fortunate that the C. neteri isolate from the colonized catheter did not infiltrate the urinary tract system, causing a more serious medical condition. The source of C. neteri in our patient remains undetermined. However, given that the patient was using a Foley catheter during the previous year without apparent incident, it is possible that catheter colonization may have been of nosocomial origin rather than community acquired as a result of gastrointestinal colonization.

To the best of our knowledge, there are only four cases reporting the clinical isolation of C. neteri (Table 1), making its occurrence even less common than C. daviseae (21 reported cases to date) and C. lapagei (16 reported cases to date). Two cases identified Cedecea species in association with ulcers (Table 1). In each case, the affected patient was either immunocompromised, had multiple comorbidities, or experienced a traumatic injury or aggressive surgical procedure, thus supporting Cedecea as an opportunistic pathogen.

C. neteri isolated from clinical specimens exhibits resistance to multiple antibiotics (Table 2). To gain insight into the potential mechanisms underlying the antimicrobial resistance phenotype, we searched the annotated genome of the representative C. neteri strain SSMD04 [14] for open reading frames (ORFs) with putative functions in antibiotic resistance. In silico analysis revealed a total of six chromosomal ORFs with sequence similarity to β-lactamases and two chromosomal ORFs with putative functions in the AmpC β-lactamase induction mechanism, namely ORF JT31_10465 and ampG (Table 3).

Based on distinctive signature motifs in the deduced amino acid sequence, we propose that ORF JT31_10470 in the SSMD04 genome is the C. neteri bla<sub>ampC</sub> gene encoding the AmpC β-lactamase. Within the deduced 382-amino-acid sequence of JT31_10470, we identified consensus sequences, S-V-S-K (positions 85–88) and K-T-G (positions 336–338), characteristic of active-site serine β-lactamases [20]. Three structural elements characteristic of class C β-lactamases [20] and a Cedecea daviseae AmpC [21] were also detected in JT31_10470: Y-A-N (171–173), D-A-E-A (238–241), and S-D-X-K (308–311). ORF JT31_10465 (876 bp), which contains a conserved DNA-binding helix-turn-helix (HTH) domain at the N-terminus, likely encodes AmpR, a LysR transcriptional regulator that controls expression of chromosomal ampC in many Enterobacteriaceae. The predicted C. neteri ampC gene (ORF JT31_10470) is located in the opposite orientation immediately upstream from the putative ampR gene (ORF JT31_10465), forming a divergent ampR-ampC operon. The presence of an AmpR homolog suggests that the C. neteri ampC gene may be inducible in response to β-lactam exposure. Consistent with the production of an AmpC β-lactamase, C. neteri clinical isolates display resistance
to ampicillin, amoxicillin, first-generation cephalosporins, and cefoxitin, and are not inhibited by the \( \beta \)-lactamase inhibitors clavulanic acid and sulbactam, but are sensitive to ceftazidime, ceftriaxone, cefepime, aztreonam, nitrofurantoin, ciprofloxacin, TMP/SMX [17].

The SSMD04 genome also contains four genes encoding putative class B metallo-\( \beta \)-lactamases (MBLs), which require zinc as a cofactor for \( \beta \)-lactam hydrolysis. For three of these ORFs (JT31_00700, 16535, and 22070), we identified the highly conserved group B-specific element H-X-H-X-D (Table 3), which is required for activity of class B \( \beta \)-lactamas [20]. MBLs catalyze the hydrolysis of a wide range of \( \beta \)-lactams, including carbapenems, whereas monobactams, such as aztreonam, are typically poor substrates for these enzymes [19]. However, \( C. neteri \) isolates reported

Table 1: Reported clinical cases involving \( Cedecea neteri \) and \( Cedecea \) sp.

| Patient (age/sex) | \( Cedecea \) sp. | Infection | Medical history | Sensitivity | Resistance | Reference |
|------------------|-----------------|-----------|----------------|-------------|------------|-----------|
| 88/M             | \( C. neteri \) | Colonized catheter | Cellulitis, hypertension, benign prostatic hyperplasia, chronic kidney disease | Piperacillin/tazobactam, cefamandole, ceftazidime, ceftriaxone, cefepime, aztreonam, nitrofurantoin, ciprofloxacin, TMP/SMX | Ampicillin/sulbactam, cefazolin, cefoxitin | Current case |
| 62/M             | \( C. neteri \) | Bacteremia | Valvular heart disease | Cefamandole, chloramphenicol, tetracycline, gentamicin, tobramycin, amikacin | Cefalothin, ampicillin, colistin | [11] |
| 27/F             | \( C. neteri \) | Bacteremia | SLE | Vancomycin | Amoxicillin, amoxicillin/clavulanic acid, aminoglycosides, cephalosporins | [12] |
| NA               | \( C. neteri \) and \( Escherichia vulneris \) | Peritonitis | Aggressive abdominal surgery | NA | NA | [13] |
| 79/M             | \( Cedecea \) sp. | Cutaneous ulcer | DM | Minocycline | NA | [15] |
| 20/M             | \( Cedecea \) sp. | Orbital cellulitis, corneal ulcer | Motor vehicle accident | NA | NA | [16] |

M, male; F, female; NA, not available; TMP/SMX, trimethoprim/sulfamethoxazole; DM, diabetes mellitus; SLE, systemic lupus erythematosus.

Table 2: Antibiotic resistance patterns of \( Cedecea neteri \) isolated from a patient’s catheter (current case) and reported in previous studies.

| Antibiotic | Susceptibility (MIC, \( \mu \)g/mL)* | Reference number | Resistance mechanism encoded in \( C. neteri \) SSMD04 genome† |
|------------|------------------------------------|-----------------|---------------------------------------------------------------|
| Aminobenzyl-penicillin | | | |
| Amoxicillin | | | |
| Ampicillin | | | |
| \( \beta \)-Lactam/\( \beta \)-lactamase inhibitors | | | |
| Amoxicillin-clavulanate | | | |
| Ampicillin-sulbactam | | | |
| Cephalosporins (1st generation) | | | |
| Cefazolin | | | |
| Cephalothin | | | |
| Cefotaxime | | | |
| Cefoxitin | | | |
| Polymyxins | | | |
| Colistin | | | |

*Intermediate (I): likely to respond to high dosage therapy. Resistant (R): unlikely to respond to high dosage therapy. †Reference [14]. ‡Analysis of open reading frame (ORF) JT31_10470 (1149 bp, 382 amino acids) in the \( C. neteri \) SSMD04 genome indicated sequence homology to AmpC \( \beta \)-lactamases. AmpC enzymes belong to the class C cephalosporinases (reviewed in [17]). Scrutiny of the deduced amino acid sequence of JT31_10470 revealed the presence of the following conserved sequence elements characteristic of class C \( \beta \)-lactamas: S-X-S-K (positions 85 to 88), Y-A-N (positions 171 to 173), and K-T-G (positions 336 to 338). §Metallo-\( \beta \)-lactamase. ¶Resistance phenotype was determined using the Kirby-Bauer disk method as reported in the cited reference.

Components of the LPS modification system (mdeB, phoP, phoQ, and the pmr operon) are present in the annotated genome of \( C. neteri \) SSMD04, but these loci do not contain mutations known to confer colistin resistance [18].
in this case and in the literature were not assessed for carbapenem susceptibility. In addition, MBLs are not inhibited by clavulanic acid or tazobactam [19]. The overlapping hydrolysis profiles of metallo-β-lactamases and AmpC β-lactamases suggest that the antibiotic resistance phenotype of C. neteri could be due to the expression of either class of β-lactamases or a combination of both. It is noteworthy that the genome of another sequenced C. neteri strain, M006 [22], also contains multiple metallo-β-lactamase genes and a putative ampC, which exhibits 93% amino acid sequence identity to the SSMD04 ampC (data not shown). In-depth functional studies, which are beyond the scope of this report, are needed to verify the specific resistance mechanisms in C. neteri.

Clinical C. neteri isolates have been reported to show resistance to colistin [11], a polypeptide of the polymyxin drug class. Genes conferring colistin resistance are associated with lipopolysaccharide (LPS) modification via cationic substitution. In Gram-negative bacteria, the PhoQ/PhoP two-component system activates expression of the pmrCAB operon, which encodes proteins responsible for cationic modifications of LPS [18]. Homology searches revealed that the C. neteri SSMD04 genome contains ngrB, phoP, phoQ, and the pmrCAB operon associated with acquired colistin resistance. No plasmid DNA was found in SSMD04, ruling out the possibility of colistin resistance conferred by the plasmid-derived mcr1 (mobilized colistin resistance) gene. However, none of the LPS-modifying genes in strain SSMD04 harbored mutations known to confer polymyxin resistance [18].

In conclusion, we report a rare case of catheter colonization by an antibiotic-resistant C. neteri strain. Genomic analysis of a representative sequenced strain identified a chromosomal AmpC β-lactamase gene that may be under induction control by an AmpR homolog, as well as the presence of multiple metallo-β-lactamase genes. Further research investigating the antibiotic resistance mechanisms of C. neteri is warranted given its increasing incidence of isolation and clinical association with severely immunocompromised patients.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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