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CASE REPORT

Catheter-Related Bacteremia Caused by Multidrug-Resistant *Leclercia adecarboxylata* in a Patient with Breast Cancer

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We report a multidrug-resistant strain of *Leclercia adecarboxylata* responsible for catheter-related bacteremia in a 47-year-old female with breast cancer. The isolated strain was resistant to several β-lactams, aminoglycosides, and folate pathway inhibitors and harbored bla_{TEM-1} and bla_{CTX-M} group 1 and *intl1* genes (*dfrA12-orfF-aadA2*) as genetic determinants for resistance. Based on a review of the *L. adecarboxylata* literature, there have been only 4 reports of antibiotic-resistant strains. To our knowledge, this is the first report of an *L. adecarboxylata* strain with simultaneous resistance to β-lactams, aminoglycosides, and sulfonamides.

CASE REPORT

A 47-year-old female was diagnosed with cancer of the right breast. Chemotherapy was administered through a peripherally inserted central catheter (PICC) inserted in the left basilic vein. Twenty days after PICC insertion, the patient developed a high fever and general myalgia. Due to her symptoms, she visited the emergency room at Chonbuk National University hospital on 29 August 2011. On admission, her blood pressure was 120/86 mmHg, pulse was 78/min, respiration rate was 20/min, and temperature was 38.4°C. Laboratory studies revealed a white blood cell (WBC) count of 2,700/ml, hemoglobin level of 11.7 g/dl, platelet count of 310,000/ml, serum creatinine of 0.67 mg/dl, aspartate aminotransferase level of 20 IU/liter, alanine aminotransferase level of 13 IU/liter, and total bilirubin level of 0.47 mg/dl. Plain abdominal erect imaging and chest computed tomography were unremarkable. The initial antibiotic therapy included cefminox sodium and isepamicin for 3 days. Her fever persisted, however, and her WBC count increased abruptly to 17,020/ml 2 days following admission. The treatment regimen was changed to cefepime, based on antibiotic susceptibility tests (AST) from blood cultures. This guided antibiotic therapy was successful and the patient became afebrile.

Initial cultures from venous and catheter blood were sampled separately, and the causative microorganism was identified as a Gram-negative bacillus. One day following admission, the catheter tip (PICC) was cultured and yielded bacteria similar to those in the blood culture by microscopic examination. The blood culture was subcultured on sheep blood agar to generate a pure colony. The isolate was identified as *Leclercia adecarboxylata* by a Vitek2 automatic identification system using a GN card (bioMérieux, Marcy l' Etoile, France). The bacteria were further identified by partially sequencing the 16S rRNA gene from genomic DNA. DNA was amplified and sequenced by Genotech (Korea). The partial 16S rRNA sequences of the isolate had 99.8% identity with *L. adecarboxylata* GTC1267 (accession no. AB273740) in the NCBI genomic database. The isolate was maintained in the Chonbuk National University Hospital Culture Collection for pathogens as KBN0601918.

The AST of *L. adecarboxylata* was investigated using the Vitek2 automatic system with the AST-N131 card and the disk diffusion method. The results are summarized in Table 1. The *L. adecarboxylata* strain was resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and most β-lactams, including narrow-, expanded-, and broad-spectrum cephalosporins, but it was susceptible to all quinolones and carbapenems tested. In addition, the strain reacted positively in a CLSI-recommended confirmatory test using cefotaxime (CTX; 30 μg), cefrazidime (CAZ; 30 μg), CTX plus clavulanic acid (CA; 10 μg), and CAZ plus CA (10 μg) discs (1).

Extended-spectrum β-lactamase (ESBL)-encoding genes were detected by 3 separate PCR assays; multiplex PCR I for bla_{TEM}, bla_{SHV}, and bla_{OXA-A}; multiplex PCR II for bla_{CTX-M} groups 1, 2, and 9; and PCR III for bla_{CTX-M} group 8/25. All PCR conditions and primer sets were described by Dallenne et al. (3). In addition, a variable region of the class 1 integron (*intl1*) gene was amplified by PCR using 5′CS and 3′CS primers, as described by Srinivasan et al. (21). All PCR products were electrophoresed on 1.0% agarose–Tris-borate-EDTA (TBE) gels containing RedSafe (iNtRON Biotechnology, South Korea) and visualized under UV light. The resulting amplicons were sequenced and identified by nucleotide BLAST on the NCBI website (www.ncbi.nlm.nih.gov). The bla_{TEM} gene amplicon had high identity (100%) with TEM-1-type β-lactamase. The bla_{CTX-M} group1 gene amplicon was 99% identical to CTX-M-3-type β-lactamases. No amplicon was detected in the PCR III assay for bla_{CTX-M} group 8/25. PCR for the *intl1* gene amplified an approximately 2-kb product. The product was sequenced, identifying 1,800 nucleotides by direct sequencing. The sequence was 98% identical to the *intl1* gene, which contains a

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TABLE 1 Antibiogram of *Leclercia adecarboxylata*

Antimicrobial agents	MIC (μg/ml)	Susceptibility
Ampicillin	>32	Resistant[a,b]
Piperacillin	>128	Resistant[a,b]
Aztreonam	16	Resistant[a]
Amoxacillin-clavulanate	16	Intermediate[a] (Susceptible[b])
Piperacillin-tazobactam	<4	Susceptible[a]
Cephalothin	>64	Resistant[a,b]
Cefazolin		Resistant[b]
Cefoxitin	8	Susceptible[a]
Cefaclor		Resistant[b]
Cefotaxime	>64	Resistant[b]
Ceftazidime	4	Susceptible[b]
Cefixime		Resistant[b]
Cefoperazone		Resistant[b]
Cefepime	8	Susceptible[a]
Imipenem	<1	Susceptible[a,b]
Meropenem	<0.25	Susceptible[b]
Amikacin	>64	Resistant[a,b]
Gentamicin	>16	Resistant[a,b]
Tobramycin	>16	Resistant[a,b]
Levofloxacin	<0.12	Susceptible[a,b]
Ciprofloxacin		Susceptible[b]
Norfloxacin		Susceptible[b]
Ofloxacin		Susceptible[b]
Pefloxacin		Susceptible[b]
Moxifloxacin		Susceptible[b]
Nalidixic Acid		Susceptible[b]
Trimethoprim-sulfamethoxazole	>320	Resistant[a,b]

[a] Vitek2 automatic system using an AST GN card.
[b] Disk diffusion test based on Clinical and Laboratory Standards Institute (CLSI) recommendations (1).

cassette array of *dfrA12-orfF-aadA2* genes from the *Enterobacteriaceae* family.

L. adecarboxylata is a Gram-negative bacillus belonging to the *Enterobacteriaceae* family. This bacterium has been isolated from environmental samples, including water and soil (23). Although it is rarely isolated clinically in humans, there are many reported cases of *L. adecarboxylata* infection in immunocompromised patients suffering from primary diseases such as cancer, leukemia, hepatoma, and renal failure (6, 11, 14, 20). In such patients, this pathogen can cause bacteremia, sepsis, peritonitis, cellulitis, endocarditis, and cholecystitis (6, 9, 11, 14, 16, 20). Its pathogenesis, specifically its entry and spread into humans, remains unclear. When considering the previous cases, bacteremia due to *L. adecarboxylata* may be closely associated with destruction of the skin barrier, such as through trauma and burn wounds, change of normal flora by antibiotic treatments, and peritoneal dialysis (2, 8, 16, 18–20). Additionally, some cases have implicated catheters as important reservoirs for bacteremia by *L. adecarboxylata*. Catheter-related bacteremia has been reported in a 69-year-old woman with leiomyosarcoma (15) and 81-year-old and 58-year-old males with end-stage renal disease (ESRD) (7, 16). Our case was similar to previously reported cases of catheter-related bacteremia (10, 16, 17), as our hospitalized patient had a PICC in place and the catheter tip culture was positive for *L. adecarboxylata*. In addition, the *L. adecarboxylata* from the catheter tip had the same biochemical and genetic profiles as the isolate cultured from the patient's blood.

Historically, this bacterium has been easily controlled with a variety of antibiotics, including aminoglycosides and β-lactams. Stock et al. (22) reported natural antimicrobial susceptibility patterns from 94 *L. adecarboxylata* strains isolated from human clinical specimens. The bacteria were naturally resistant to penicillin G, oxacillin, erythromycin, roxithromycin, clarithromycin, ketolides, lincosamides, streptogramins, glycopeptides, rifampin, fusidic acid, and fosfomycin but susceptible to tetracyclines, aminoglycosides, most β-lactams, quinolones, folate pathway inhibitors, chloramphenicol, nitrofurantoin, and azithromycin. These patterns were present in many clinical *L. adecarboxylata* infections. On the other hand, Yao et al. (24) reported resistance to aminoglycosides, quinolones, amaphenicols, and trimethoprim-sulfamethoxazole in *L. adecarboxylata* isolated from a pig farm. These antibiotic susceptibility phenotypes clearly differed from the present *L. adecarboxylata* strain. For example, the current strain was resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and most β-lactams, including narrow-, extended-, and broad-spectrum cephalosporins. In addition, the strain produced ESBL. To our knowledge, this is the first report of a multidrug-resistant *L. adecarboxylata* strain in human that produces ESBL. Due to antibiotic resistance, initially administering cefminox sodium (a narrow-spectrum cephalosporin) and isepamicin (an aminoglycoside) resulted in treatment failure. Based on AST results, intravenous cefepime was administered 3 days after admission, resolving the bacteremia. Therefore, appropriate therapy for *L. adecarboxylata*-induced bacteremia should be based on AST results.

Antibiotic-resistant *L. adecarboxylata* strains have been reported in 4 different cases (Table 2). Of these cases, only 1, isolated from a patient with leukemia, produced ESBL. This strain encoded SHV-type β-lactamases (17). Laboratory investigations, however, did not detect genetic determinants of antibiotic resistance from any prior resistant strains, except for strains carrying the bla_{SHV} gene (4, 5, 11). In this case, we identified genes encoding TEM- and CTX-M group 1-type β-lactamases. In addition, this strain harbored *intI1* with *dfrA12* and *aadA2* genes, which encode dihydrofolate reductase and aminoglycoside-3′-adenyltransferase responsible for trimethoprim-sulfamethoxazole and aminoglycoside resistances, respectively (10, 12, 13). To our knowledge, there have been no reports of *L. adecarboxylata* strains simultaneously carrying bla_{TEM-1}, $bla_{CTX-M-3}$, and *intI1* genes until recently. These genes have been frequently detected in Gram-negative bacteria from human clinical specimens, as well as environmental sources, such as food, domestic animals, water, and soil, in a number of countries, including Korea (10, 12, 13). Since these genes are located on mobile genetic elements, resistance could be easily transferred (10, 12, 13). Although *L. adecarboxylata* has been recognized as a relatively unimportant human pathogen due to its low virulence and high antibiotic susceptibility, multidrug-resistant strains can become life-threatening human bacterial pathogens by acquiring genetic determinants, including bla_{SHV}, bla_{TEM-1}, bla_{CTX-M} group 1, and *intI1* genes.

In conclusion, we report the first case of catheter-related bacteremia due to ESBL-producing a multidrug-resistant *L. adecarboxylata* strain harboring bla_{TEM-1}, $bla_{CTX-M-3}$, and *intI1* cassette (*dfrA12-orfF-aadA2*) genes in a 47-year-old female with breast cancer.

Nucleotide sequence accession numbers. Partial sequences of the *L. adecarboxylata* KBN0601918 strain have been submitted to GenBank under the following accession numbers: JX129231 for the partial 16S rRNA gene, JX129229 for partial bla_{TEM-1}, JX129230 for $bla_{CTX-M-3}$, and JX129228 for *intI1*.

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TABLE 2 Antibiotic-resistant *L. adecarboxylata* isolated from humans[a]

Age (yr)	Sex	Underlying disease	Primary focus	Specimen	Antibiotic resistance	Genetic determinants of resistance	Therapy	Coinfection	Outcome	Reference
42	F	MM	Central line	Blood	Fosfomycin	ND	Cloxacillin	No	Recovery	5
58	M	AML	Unknown	Blood	ESBL	bla_{SHV-12}	Cefuroxime	No	Recovery	17
80	F	CBG, candida sepsis	Unknown	Blood	Ampicillin	ND	Ciprofloxacin	*E. faecalis*, *E. hermannii*	Recovery	4
71	M	Hepatoma	SBP	Blood, peritoneal fluid	Ampicillin	ND	Cefoperazone, ciprofloxacin	No	Death	11
47	F	Breast cancer	Catheter	Blood	ESBL, aminoglycosides, Stx	bla_{TEM-1}, bla_{CTX-M} group 1, *intI1* (*aadA2*, *dfrA12*)	Cefepime	No	Recovery	This study

[a] MM, multiple myeloma; AML, acute myelogenous leukemia; CBG, coronary artery bypass graft; SBP, spontaneous bacterial peritonitis; F, female; M, male; Stx, trimethoprim-sulfamethoxazole; ND, not done.

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